Procter&Gamble

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway, Cincinnati, Ohio 45241-9974

September 18, 2001

Docket Management Branch
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, Maryland 20857

Re: **Correction to Page One of the Citizen Petition to Amend the Tentative Final Monograph for Health Care Antiseptic Drug Products for Over-the-Counter Use; Docket 75N-183H**

Dear Sir/Madam:

This letter is being sent to correct a typographical error on page one of the Citizens Petition referenced above, dated 9/05/01. This petition was received by the Dockets Management Branch on 9/06/01 and assigned docket number 78N-0038/CP14.

The docket number referenced on the original page one, 78N-0038, was in error. The correct number is 75N-183H.

Your attention to this matter and subsequent reassignment of a docket number to the Citizens Petition is very much appreciated.

Sincerely,

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CP8

75N-183H

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Procter&Gamble

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September 5, 2001

Docket Management Branch
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, Maryland 20857

Re: **Citizen Petition to Amend the Tentative Final Monograph for Health Care Antiseptic Drug Products for Over-the-Counter Use; Docket 78N-0038**

Dear Sir/Madam:

The Procter and Gamble Company submits this petition under 21CFR §10.30, to request the Commissioner of Food and Drugs to take the following action on proposed 21CFR §333, June 14, 1994, the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products for Over-the-Counter Use (59 FR 31401) to:

> **Include salicylic acid as a Category I generally recognized safe and effective antibacterial active ingredient, for the following product categories from the Health Care Continuum Model (HCCM): consumer hand product, food handler product, and health care personnel hand product.**

On June 13th, 1995, the Cosmetic, Toiletry and Fragrance Association (CTFA) and the Soap and Detergent Association (SDA) submitted comments to the TFM. These included the HCCM proposal, which proposes a framework for the the regulation of topical antimicrobial drug products consistent with public health needs in domestic, institutional and industrial settings.

A. Action Requested

Petitioner requests that the Commissioner amend proposed 21CFR §333 to include salicylic acid as a Category I generally recognized as safe and effective antibacterial active ingredient for use as follows:

- Include salicylic acid as a Category I, generally recognized as a safe and effective antibacterial active ingredient for use in **consumer hand products, food handler products, and health care personnel hand products.**

- Include salicylic acid as a Category I antibacterial active ingredient for use in these products at **levels of 1.0 - 1.2 percent in non-rinse off applications, and 2.0 - 3.5 percent for products to be rinsed with water.**

- Include labeling that allows salicylic acid formulations to make **antibacterial indications.** For non-rinse products containing salicylic acid as the active ingredient, placement of additional warning statements are recommended that say:

  - "Do not use this product on children under 12 months of age"
  - "For use on hands only"

The proposed antibacterial labeling for consumer hand products, food handler products, and healthcare personnel hand products, as recommended by CTFA/SDA is in Attachment I.

B. Statement of grounds

CONSIDERATION OF PETITION

Salicylic acid was an active ingredient in OTC drug products marketed in the U.S. before May 11, 1972, prior to establishment of the OTC Drug review process and monograph system.

In the U.S., salicylic acid is an established OTC monograph ingredient which has a long history of both drug and cosmetic use. Salicylic acid USP is a Category I active ingredient for leave-on applications (acne, warts, corns and calluses) and rinse-off applications (dandruff), and for applications that can be either leave on or rinse off (seborrheic dermatitis and psoriasis). Salicylic acid products have been marketed for a material time, and to a material extent, for treatment of acne, warts and dandruff, all conditions which include an antimicrobial component and are therefore essentially similar to the topical antimicrobial use proposed in this Citizen Petition. Moreover, salicylic acid has an established history of use in topical antimicrobial products outside the United States. In Canada, salicylic acid is regulated by the Canadian Health Professionals Board as a Category IV monograph OTC drug and approved for use as an antibacterial active ingredient in antiseptic skin cleansers at a usage level of 0.5 to 3.5 percent in rinse off and non-rinse off product forms. In Japan, salicylic acid is approved for use in several quasi-drugs including anti-acne treatments and corn/callus removers, and as an antibacterial active ingredient in rinse-off medicated skin cleansers up to 2.0 percent. In Argentina and Brazil, salicylic acid is approved for use in anti-acne treatments at 2.0 percent, and in anti-dandruff products at a 3.0 percent usage level.

Pursuant to Section 201 (p) of the Federal Food and Drug Act, salicylic acid is not a "new drug" requiring submission of New Drug Application (NDA). This petition is being submitted to amend the Tentative Final Monograph for Health Care Antiseptic Drug Products, published in 59 FR 31401, June 17, 1994 to include salicylic acid as a Category I active ingredient for use in consumer hand products, food handler products, and health care personnel hand products.

Salicylic acid is known to provide keratinolytic activity and is currently approved for similar topical uses as an active ingredient in products used daily and/or repeatedly on the skin for the treatment of dandruff, acne, warts, corns and calluses.

These OTC drug products have been safely marketed for over 20 years, and for over 10 years have been included in finalized monographs developed under the OTC review process. This precedent, together with its use in topical antimicrobials outside the United States, warrants consideration of salicylic acid for an extended OTC monograph condition of use in antiseptic skin cleansing products.

PROVEN SAFE MARKETING

Salicylic acid is historically proven to be safe in U.S. marketed OTC drugs that are topically applied to the skin on a repetitive, chronic basis. In other parts of the world it is approved for use as an active ingredient in medicated/antiseptic skin cleansers sold in mass markets, and for broad use in cosmetic applications. This safe marketing experience, combined with the significant amount of human safety data that exists for salicylic acid warrants its consideration of Category I status.

Subsequent to the OTC Drug Review process beginning May 11, 1972, salicylic acid has been included in finalized monographs for conditions that deem it to be generally safe and effective as an active ingredient for the following indications of use: the treatment of acne, the control of dandruff, seborrheic dermatitis and psoriasis, and the removal of corns, calluses and warts (Table 1). An OTC Drug Review Panel also concluded that salicylic acid is safe as an antifungal treatment for athlete's foot, jock itch and ringworm, although during final rulemaking (58 FR 49890, September 23, 1993) an insufficient amount of efficacy data was available for these conditions to include it as a monograph ingredient. The concentrations of salicylic acid proposed for use in antimicrobial skin cleansing products do not exceed a concentration higher than what is currently marketed, nor what was marketed prior to December 4, 1975 (a requirement for recommendation under the OTC Drug review referenced in 21CFR §330.13(a)(2)).

Table 1 Final monographs That Include Salicylic Acid

Citation		Indication of Use
56FR41008	§333.310, §333.350	Active ingredient for the treatment of acne, 0.5-2.0%
56FR63568	§358.710, §358.750	Active ingredient for control of dandruff, seborrheic dermatitis, and psoriasis, 1.8-3.0%
55FR33261	§358.510, §358.550	Active ingredient for the removal of corns and calluses, 12-40% according to vehicle
55FR33261	§358.110, §358.150	Active ingredient for the removal of warts, 5-40% according to vehicle

In addition to health care preparations, salicylic acid has been shown to be safe and effective for its use as a daily skin exfoliant and skin conditioning agent in several topically applied cosmetic formulations sold globally, including facial cleansers, astringents and moisturizers at concentrations ranging from 0.0008 to 3.0 percent. Within the European Union, a safety dossier (Appendix A) has been prepared and submitted to the Scientific Committee on Cosmetic Products and Non-Food Products to extend the use of salicylic acid from preservative use in cosmetic products to use as a cosmetic ingredient in skin care products and non-rinse off hair care preparations up to 2.0% and 1.0% respectively.

HUMAN ASSESSMENT OF SAFETY

The FDA has previously prepared and reviewed safety data on Salicylic Acid (SA) as part of various monograph processes. The references for these monographs as well as the concentration of salicylic acid previously approved by the FDA are sited in the preceding section in Table I. The conclusion reached in each of these monographs was that salicylic acid is safe and effective for the intended indication. For convenience and brevity, the safety review portion of these monographs can be found in Appendix B. The inclusion of this safety data (Appendix B) is relevant as the levels of salicylic acid which are here petitioned to be deemed safe for use in antibacterial products range from 1.0-1.2% for non-rinse applications and 2.0-3.5% for products to be rinsed with water.

The Expert Panel of the Cosmetic Ingredient Review (CIR) has also published a final report on the general physical properties and safety of salicylic acid in cosmetic products. The general toxicology information is summarized here, but the reader is referred to Appendix C for more detail.

The oral LD_{50} for salicylic acid in rats was found to be 0.89 g/kg and the dermal LD_{50} for rats was reported to be >2 g/kg. The dermal LD_{50} for mice was reported to be 0.5 g/kg. A local lymph node assay to detect sensitization indicated that concentrations of less than 20% salicylic acid led to no evidence of sensitization in the mice. Human sensitization potential was investigated with 2% salicylic acid containing gel, and results indicated no evidence of delayed contact hypersensitivity. Numerous *in vitro* and *in vivo* teratogenicity studies have been performed on salicylic acid and salicylate derivatives, mostly with positive results. Salicylic acid is considered non-mutagenic and demonstrated no effects on mitosis or chromosome integrity and was reported to be non-carcinogenic. Special investigations included findings that salicylic acid was negative for photosensitization in mice. Also, 2% salicylic acid (in a gel formulation) was reported to be non-phototoxic and non-photo allergenic in humans. Salicylic acid was reported to exhibit keratolytic action.

After reviewing the scientific literature, the CIR Expert Panel concluded that "these ingredients are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection." It is important to note that this concern over sun sensitivity is an opinion based mainly on data generated for alpha-hydroxy acids and the concern related to increased keratolytic action. It is worth noting that even though salicylic acid is a UV absorber, there is no evidence that it is activated. The data cited in the CIR regarding negative findings in photoxicity and photoallergenicity tests with 2% salicylic acid further supports this statement. Furthermore, derivatives of salicylic acid are recognized for their skin protective effects, i.e. octylsalicylate and trolamine salicylate, at levels of five percent and twelve percent respectively, are recognized by the FDA as UV protectants (21CFR 352.10 (k)(q)). For these reasons, it is our belief that the CIR Expert's panel opinion on sun sensitivity should not impact safety based labeling of the proposed salicylic acid containing antibacterial products.

Since Appendices A, B and C contain a great deal of information related to chemistry, biochemistry and general safety information on salicylic acid, the purpose of this safety review will be to include the relevant toxicological data as it relates to the safety rationale behind the petitioned concentrations. There are three areas of toxicological concern when exposing humans to salicylic acid. They are: 1) Salicylicism, 2) Reproductive Toxicity and 3) Reyes Syndrome. These will be addressed both generally and in relation to the salicylic acid concentrations petitioned here.

Background:

Aspirin is acetylsalicylic acid (ASA), which is readily hydrolyzed in the stomach to salicylic acid. A great deal of scientific literature exists for aspirin and this information is relevant to topically applied salicylic acid (reviewed in references 1,2). Aspirin is a frequently used oral analgesic and antipyretic agent. Typical uses of aspirin include:

50 - 150 mg/d (prevention of pregnancy induced hypertension)
325 - 1000 mg/d (prevention of thrombosis)
650 - 1300 mg/d (headaches, antipyretic)
5000 -6000 mg/d (rheumatic disease)

Once absorbed, salicylates are rapidly distributed throughout the extracellular fluid and most body tissues. High concentrations occur in the liver and kidney. Albumin and other plasma proteins can bind up to 50-80% of the salicylic acid in plasma and it is only the free drug that exerts pharmacological activity. The plasma half-life for salicylates is 2 – 3 hours in low doses and about 12 hours at anti-inflammatory doses. In young children (<10 years) where plasma albumin levels are lower than adults, the total concentration of salicylic acid in the blood may be low, but more of the drug is available in the free state and therefore concentrates in the tissues. Salicylates can cross the placental barrier and neonates born to mothers who ingest aspirin prior to labor may have high salicylate serum levels. Elimination of salicylates is also lower in the infant due to the immaturity of the renal excretory and glucuronide conjugation pathways. Salicylates inhibit prostaglandin synthesis, it is this inhibition that is believed to be linked to the pharmacological effects.

Salicylicism

The signs and symptoms of salicylic acid intoxication vary according to the susceptibility of the individual. Children are particularly susceptible to intoxication due to their small extracellular fluid volume relative to the potential surface area for treatment (3). Renal function also plays a key role as the plasma concentration of salicylate is increased by conditions such as renal disease that decrease glomerular filtration rate or reduce its secretion by the proximal tubules (4). As discussed in the FDA monographs, chronic salicylate toxicity can result from long-term exposure to salicylate at doses of 12.2 mg/100 mls blood or greater (47 FR 54660, December 3, 1982). The primary effects manifest are: tinnitus, hearing loss, dimness of vision, headache, dizziness, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, increased heart rate, nausea, vomiting and occasionally diarrhea. Acute salicylate overdose has symptoms similar to those of chronic intoxication, but the effects are often more pronounced with acid-base disturbances, dehydration, fever and hyperglycemia or hypoglycemia manifest. A benchmark for toxicity used previously by the FDA is 30 – 50 mg SA/100 ml blood (based on a total of 7 Litres blood; 47 FR 12549, March 23, 1982). This level is considered toxic with severe reactions including: drowsiness, confusion, difficulty breathing and hemorrhage. Treatment of salicylicism is mainly symptomatic and supportive therapy consisting of removal of the salicylate typically from GI tract, correction of fluid, electrolyte and acid-base disturbances and measures to enhance salicylate elimination.

The concentration of salicylic acid petitioned here for non-rinse application (1.0 -1.2%) poses no concerns of salicylicism to consumers. Although the FDA has used 30 – 50 mg/100 mls blood as a benchmark for salicylicism in previous monographs, 12.2 mg/100 mls has been identified in

these same monographs as the effect level for first signs of salicylicism. Since children could potentially use a salicylic acid containing antibacterial product this lower number was used for conservatism. Exposure and risk assessments were conducted for the worst-case scenario (Attachment IIa). The predicted blood level following a one time use of a leave-on salicylic acid containing antibacterial product would be anticipated to result in a blood level of 0.66 mg/100 mls blood for a 1-year old child. This blood level is 18.5 fold below the effect level benchmark. If a child were to use such a product even ten times per day, the blood level would still remain below this effect level. Since the half life of salicylic acid is relatively short (2-3 hours), even this excessive use of product would not be expected to pose a safety risk. Since the blood volume of an adult is much larger than a child no safety risk is anticipated for adult use (estimated blood levels would be approximately 0.07 mg SA/ 100 mls blood for an adult with a 7L blood volume). Because serious misuse (such as whole body use) of a leave-on product could result in blood levels of salicylic acid approaching the benchmark for first signs of salicylicism, it is recommended that a warning be applied to all leave on products and that age be restricted by the following label: "Do Not Use This Product on Children Under Twelve Months of Age" and "For Use on Hands Only."

Using the same rationale stated above, the benchmark of 12.2 mg/100mls was used for assessing the safety of a rinse off application containing 2.0-3.5% salicylic acid (Attachment IIb). The predicted blood level following a one time use of 10 grams of a rinse off product containing salicylic acid would be anticipated to result in a blood level of 0.19 mg/100 mls blood. This blood level is 64 fold below the effect level benchmark. A 10 gram per day scenario suggests numerous hand washes or a misuse as body wash application. Even an excessive use of such a rinse off product (particularly since the half life of salicylic acid is relatively short 2-3 hours) would not be expected to pose a safety risk. Since the blood volume of an adult is much larger than a child no safety risk is anticipated for adult use (estimated blood levels would be approximately 0.02 mg SA/ 100 mls blood for an adult with a 7L blood volume). Because of the large margin of safety no warning labels are suggested for non-rinse off products.

Reproductive Toxicity

Reproductive toxicity has been associated with aspirin administered orally. Evidence from animal studies and limited retrospective clinical studies suggest that aspirin ingestion during the latter portion of gestation can have adverse effects on both the mother and the fetus. These effects include: prolonged labor and gestation, postpartum hemorrhage of the mother, hemorrhage in neonates and congenital malformations in newborns. The congenital malformations have only been reported in animal models and are believed to be species specific. High doses of aspirin (3200 mg/d) late in pregnancy have been shown to delay the onset of labor, increase delivery complications and increase the likelihood of postpartum hemorrhage (5,6). However, it should be noted that those reports were studies of mothers with muscoskeleteal disease. In six independent clinical trials in which low dose aspirin (10-150 mg/d) was administered during the second and third trimesters of pregnancy for the treatment of preeclampsia, there was no evidence of aspirin related adverse effects on mother or on the newborn (7). Furthermore, maternal treatment with very low doses of aspirin during 2^{nd} and 3^{rd} trimesters of pregnancy has been used for the prevention of fetal growth retardation, pregnancy-induced hypertension and stillbirth in high-risk pregnancies.

Absorption of salicylic acid from topically applied products has been demonstrated (8, 9, 10). Salicylic acid absorption from a lotion is expected to be $\geq$ 44% based on published analytical work (11). Percutaneous absorption of salicylic acid is dependent on vehicle of application, pH,

skin hydration, number of applications and skin condition. Because absorption of salicylic acid from a topically applied product can be on the order of 44%, systemic loads must be understood. For comparison purposes, the systemic load of salicylic acid resulting from use of a topical exposure can be compared to the systemic load of salicylic acid resulting from the ingestion of one baby aspirin (81 mg acetylsalicylic acid = 62 mg SA) which is the amount of ASA considered appropriate for adult pregnant women. This is based on the information in the Teratogen Information Service database which is designed to assist physicians or other healthcare professions in assessing the risk of possible teratogenic exposures in pregnant women. According to the information in this database, one baby aspirin can be ingested daily by a pregnant woman with no evidence of maternal or fetal toxicity . Exposure and risk assessments for this reproductive toxicity endpoint are addressed in Attachment IIIa.

The concentration of salicylic acid petitioned for non-rinse application (1.0 -1.2%) poses no concerns of reproductive risk to consumers. The benchmark used for risk assessment purposes was based on the Teratogen Information Sevice Database which reports that one baby aspirin is safe for pregnant women. One baby aspirin contains 81 mg of ASA and the corresponding amount of salicylic acid formed following hydrolysis of ASA in the stomach would be 62 mg. If 62 mg of salicylic acid were in the blood of an adult pregnant female weighing 58 kg, the systemic load would be 1.07 mg/kg/d. An adult pregnant female using a non-rinse antibacterial product containing up to 1.2% salicylic acid would be anticipated to have a systemic load of 0.09 mg/kg/d. Thus the systemic load from the antibacterial product would be less then that resulting from ingestion of one baby aspirin. Even up to 10 uses of antibacterial product containing 1.2% salicylic acid would not be expected to result in any risk to mother or baby. Additionally, in a multiple use scenario, since the half-life of salicylic acid is relatively short 2-3 hours, even this excessive use of product would not be expected to pose a safety risk. No safety related warning label is recommended regarding this endpoint

Using the same rationale stated above, the benchmark of one baby aspirin ingested by a pregnant female resulting in a safe systemic load of 1.07 mg/kg/d was used for assessing the safety of a rinse off application containing 2.0-3.5% salicylic acid (Attachment IIIb). An adult pregnant female using a rinse-off antibacterial product containing up to 3.5% salicylic acid would be anticipated to have a systemic load of 0.03 mg/kg/d. Thus the systemic load from the antibacterial product would be less then that resulting from ingestion of one baby aspirin. Even up to 10 uses of antibacterial product containing 3.5% salicylic acid would not be expected to result in any risk to mother or baby. Additionally, in a multiple use scenario, since the half-life of salicylic acid is relatively short (2-3 hours), even this excessive use of product would not be expected to pose a safety risk. No safety related warning label is recommended regarding this endpoint.

Reyes Syndrome

Reyes syndrome was first characterized as a distinct entity in 1963 by Dr. R. Douglas K. Reye, M.D and his colleagues in Australia and also by Dr George Johnson, M.D. and his co-workers in the U.S. (12, 13). The syndrome was characterized by a prodromal viral illness followed by (3-5 days later) an acute onset of vomiting, disorientation, seizures and loss of consciousness (14,15,16,17). All cases of Reyes are believed to result from acute mitochondrial dysfunction (18, 19). The suspected causes of Reyes syndrome arise from any of the following four main groups: infection, toxic insult, inborn errors of metabolism or hypoxia (20, 21). Examples of each of these are given in Table I, Attachment IV.

The causal relationship between salicylates and Reyes remains controversial, but the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA), the American Academy of Pediatrics Committee on Infectious Diseases and the Surgeon General all advise against using aspirin (acetylsalicylic acid) in children and teenagers with influenza or chickenpox. In the USA, Reyes occurs most commonly among children between the ages of 5 and 15 years (average age 11 years with 12-15 year olds most commonly affected). A diagnosis of Reyes has become relatively rare in children under the age of 3 and most of the earlier reported cases in this age group may be the result of misdiagnosis of inborn errors of metabolism (22).

Acetylsalicylic acid (ASA) exerts its pharmacological action through two entirely separate pathways (23). Once absorbed, ASA is converted by hydrolysis to salicylate and acetate. Following this conversion, the activated acetyl group acetylates a number of important enzymes, which are involved in the biosynthesis of very powerful biologic mediators. An assumption that ASA association with Reyes is through the salicylate pathway ignores the most important pharmacologic pathway of ASA – acetylation. A case can be made that the acetylation pathway of ASA is at least as likely as the salicylate pathway to be associated with Reyes. As early as 1962, an association between ASA and the development of Reyes was suggested. This hypothesized association was predicated on the fact that salicylate intoxication can also result in hepatic dysfunction and encephalopathy (24, 25) Additionally children with Reyes who died or had substantial neurological complications had significantly high serum salicylate levels (26).

Several epidemiological studies conducted in both the US and Great Britain between 1978 and 1989 suggested a close relationship between the treatment of children with ASA for viral infections and the subsequent development of Reyes (27,28,29,30,31,32). Conversely, the relationship of ASA usage to the development of Reyes has been questioned because there are several case reports of children who have developed Reyes and had no history of prior ASA ingestion (26, 33, 34). In addition, Reyes is prevalent in countries such as Great Britain and Australia where acetaminophen is used in place of ASA for the treatment of influenza and varicella (35,36).

It is important to weigh the assertion that ASA ingestion during an antecedent viral illness is strongly associated with Reyes with the fact that no epidemiologic study has shown an association between non-acetylsalicylic acid (NASA) salicylates and Reyes. This suggests that if there is a causal association with ASA, it is not salicylate but rater the acetylating action of ASA that may be implicated in Reyes. Furthermore, ASA has been used widely throughout the past century, therefore the sudden appearance of Reyes suggests either an alteration in host receptivity or a new causative agent.

In summary, there are no epidemiological, pharmacological, and biochemical data to support the hypothesis that metabolism of ASA to salicylate is the cause for the association between Reyes and ASA that have been reported in epidemiologic studies. No association has been found between Reyes Syndrome (RS) and NASA salicylates through any of the epidemiolgic studies. Biochemical studies have shown that ASA evokes pharmacologic and toxicolgic effects through two pathways – acetylation and salicylate – with many important biochemical effects being through the acetylation pathway. ASA and NASA salicylates have been shown to have many pharmacologic and toxicologic differences that are attributable to acetylation by ASA. To date, there is no factual basis for speculating that salicylates in general would be associated with RS. However, for risk assessment purposes it would be appropriate to assume that the lowest dose of ASA a child could be exposed to and possibly have exhibited Reyes like effects would be that found in one baby aspirin. Such an assessment is shown for non-rinse and rinse-off applications of salicylic acid in an antibacterial product in Attachment Va and Vb respectively.

The US Public Health Service (USPHS) Study of Reye's Syndrome and Medications reported that one baby aspirin was the lowest concentration of ASA reported as ingested and found to be associated with Reyes – where a 3 year old is the youngest child and one baby aspirin is the smallest dose (Hurwitz et al., 1987). The concentration of one baby aspirin is known to be 81 mg ASA that is hydrolyzed in the stomach to 62 mg salicylic acid. If the body weight of a 3-year old child is considered in relation to the 62 mg salicylic acid ingested, the systemic load is estimated to be 4.13 mg/kg. When this value (4.13 mg/kg) is compared to the estimated systemic load from one use of a non-rinse salicylic acid containing antibacterial product (0.53 mg/kg) a 7.7 fold difference in systemic loads is indicated (Attachment VI). It would follow that up to 8 daily uses of such an antibacterial product on a 1-year old child could lead to systemic loads of salicylic acid which approach the equivalent value for ingestion of one baby aspirin. Additionally, when this systemic load is compared to the estimated systemic load from a salicylic acid containing rinse off antibacterial product under multiple uses or a misuse as a body wash scenarios a 23 fold difference in systemic loads is indicated (Attachment VI-a). The risk associated with these systemic loads is put in perspective when the following statements are considered. The USPHS concluded that "Analysis of the independent risk of ASA and non-acetylsalicylic acid (NASA) salicylates revealed a significant association with ASA; the independent risk of NASA salicylates could not be assessed because only two cases were not exposed to ASA". The FDA, following its review of available data, issued a rule on June 9, 1988 to extend its requirement for Reyes labeling of oral and rectal ASA and ASA-containing products (21 CFR 201.314). In concluding that Reyes labeling should not be extended to NASA salicylates, the FDA stated in part, "FDA notes that the scientific research to date (1988) on which the Reyes warning statement requirement is based, focuses on the association between Reyes and ASA, rather than on the broader category of drug products containing non-acetylsalicylic acid salicylates. Indeed, the USPHS study reported that there were too few subjects with reported exposures to non-acetylsalicylic acid salicylates for a meaningful analysis." These statements and other studies support the belief that NASA salicylates are not associated with Reyes (31, 37, 38). For these reasons, children exposed to an antibacterial non-rinse or rinse-off application would be anticipated to be at no risk of enhanced likelihood of developing Reyes Syndrome and thus no label suggesting avoidance of the product when experiencing flu like conditions is recommended.

The frequency, duration and type of reported adverse events that have been associated with marketed products containing salicylic acid are typical of products used to treat or cleanse the skin, and further support its safety in use.

Post market surveillance reports of adverse effects associated with salicylic acid products were collected from three reporting systems including FDA's Spontaneous Reporting System (1969 – 1997), FDA's Adverse Event Reporting System (1997 – 2000), and Procter & Gamble's Beauty Care Safety Surveillance System (1997 – 2000). A summary of these adverse events is included in Attachment VI and the printed reports are included in Appendix D. The majority of reported adverse effects that were considered suspect in their association with salicylic acid products were symptoms of acute, transient dermatitis. These responses were primarily skin irritation or other dermal conditions, e.g. acne and unknown sources of cuts and scratches, presumably from packaging containers. There were reports of accidental ingestion, inhalation effects, and eye irritation from direct or indirect contact with the eyes. No serious adverse effects were reported, and a qualitative/quantitative evaluation of the reported events shows that they are consistent with other topically applied products currently in use, or generally for new products recently introduced to the marketplace.

SALICYLIC ACID IS EFFECTIVE AGAINST A WIDE RANGE OF MICROORGANISMS

Salicylic acid is part of a phenolic group of benzoic acid derivatives that are largely responsible for antibacterial activity. This activity is achieved through a mechanism of action that attacks the plasma membrane of bacteria and inhibits some enzyme systems. Only the dissociated part is active, this is 90% at pH2, 8.6% at pH 4 and 0.9% at pH6 (39) (40). According to published literature summarized below, salicylic acid was found to be a rapid, effective agent against a broad spectrum of microorganisms including strains of gram negative and gram positive bacteria, yeast and rhinovirus. Evidence of antibacterial efficacy *in vitro* and *in vitro* was shown in internal tests conducted with two salicylic acid product formulations (rinse off and non-rinse off) that were developed for consumer end use, but not optimized to provide broad spectrum antimicrobial efficacy. As shown in Attachment VII these formulations contain common personal cleansing surfactants, skin conditioners and buffers. It is expected that if salicylic acid is accepted in the Final Monograph as a Category I active ingredient that product formulations intended for market world be optimized for antibacterial activity. This concept is recognized in Comment C.6 in the Tentative Final Monograph for Health Care Antiseptic Drug Products (59 FR 31401, June 17, 1994) where it is stated, "Although the Category I active ingredients currently included in this amended tentative final monograph are broad spectrum independent of formulation, some Category III antiseptic ingredients have limited spectra, ... but when properly formulated in a final product the spectrum can be broadened to include additional activity against microorganisms, thereby possibly enabling these ingredients to become Category I ingredients."

The test methods used internally to determine the activity of salicylic acid and product formulations containing salicylic acid, plus all performance criteria, are based on Industry Coalition's Proposal for Finished Product Efficacy Testing prepared by CTFA/SDA and submitted to Docket 75N – 183H on September 29, 1999. As part of the HCCM, this proposal encourages the use of standard American Society for Testing Materials (ASTM) methods to better reflect actual product use conditions, and to have the flexibility of being updated to reflect appropriate scientific developments.

Antimicrobial Efficacy -Published Studies

The effectiveness of salicylic acid against a broad spectrum of microorganisms including various strains of bacteria, yeast and mold has been established in **minimum inhibitory concentration (MIC) tests** and summarized in Attachment VIII. The bactericidal and antimycotic activity of salicylic acid was assessed and compared to undecylenic acid, and two hydroquinolin derivatives in a study conducted in Switzerland by CIBA Laboratories (41). Using a modified Bryson and Skybalski gradient plate test, MICs were measured using a broad range of dermatophytes, gram positive and gram negative bacteria strains, and yeasts isolated in a university dermatological clinic. Results showed salicylic acid was able to inhibit the entire spectrum of twenty pathogens at ranges from 70 to 3000 ug/mL. From these experiments it was concluded that salicylic acid would have a very rapid microbiocidal effect at concentrations equal to those formulated in products intended for topical applications, estimated at a three percent usage level. Separately, in published references, MICs at pH 3 have been reported to be in the range of 1250–2500 ug/l (39).

Independent clinical studies conducted in Germany support the antimicrobial activity of salicylic acid on the skin. The antimicrobial efficacy and bioavailability of salicylic acid was evaluated by Albert Hartmann of the Department of Dermatology, Bavarian Julius-Maximilian University of Warzburg (42). By measuring the normal flora of the forehead via a method called the Standard Forehead Skin Test (SFST), the short term and long term efficacy of topically applied antimicrobials were compared including 60% isopropanol, 60% n-propanol, povidone iodine (aqueous solution), and 3% salicylic acid with 1% liquid phenol in 50% isopropanol. Compared to 60% n-propanol (a reference substance for surgical skin disinfectants by the German Society for Hygiene and Microbiology), the salicylic acid tincture showed equal reduction in immediate bacterial density. However, the salicylic acid tincture showed longer persistence, up to 24 hours, vs. n-propanol which showed a complete regeneration of bacteria in the same time period. A modification of the method to simulate a twice daily application at twelve hour intervals demonstrated significant cumulative antimicrobial effects that can be attributed to salicylic acid as shown by comparison of salicylic acid/isopropal alcohol (IPA) to liquid phenol/IPA and to the complete tincture.

In-vitro studies conducted jointly at the North Shore University Hospital, New York University School of medicine and Framingham State College, have investigated the mechanism of action of salicylic acid on *Staphyloccus epidermis*, a gram positive bacterium found on the skin (43). The inclusion of 5mM salicylic acid in medium inhibited both growth and biofilm production of *S. epidermis* by up to 55% due to reduction in the production of biofilm components.

Bacterial **resistance and susceptibility** to antibiotics impacted by salicylate was recently researched at the Chicago College of Osteopathic Medicine and Curtin University in Australia (44). Salicylate was shown to reduce the production of various factors bacteria use to mediate infection, act as an antimicrobial, and cause a reduction in intrinsic resistance to certain types of bacteria. It was also shown to induce an intrinsic multiple antibiotic resistance mechanism in many types of bacteria. However, these findings were inconclusive in determining the potential decrease or increase in the efficacy of antibiotic therapies by non-steroidal anti-inflammatories *in vivo*.

A study conducted in Italy at the University of Naples determined that sodium salicylate and acetylsalicylate, derivatives of salicylic acid do not interfere with antimicrobial therapy of gram negative porin deficient bacteria by two different antibiotics. Neither sodium salicylate nor acetylsalicylate altered the Minimum Inhibitory Counts (MICs) or Minimum Bactericidal Counts (MBCs) of mezloacillin or ciproflaxacin vs. *P. aeruginosa, S. marcescens and P. vulgaris* (45).

Antibacterial resistance to antibiotics used for acne therapy was investigated by E. Anne Eady of the University of Leeds in the U.K. In a published report, she expressed no concern that salicylic acid, as an OTC anti-acne treatment, contributed to antibacterial resistance. Furthermore, it was suggested that antibacterial resistance to oral antibiotics used to treat acne could be reduced through the concomitant use of a non-antibiotic antimicrobial on the skin such as salicylic acid, by eliminating the sensitive strains of resistant coagulase-negative staphylococci (46).

Antibacterial Efficacy *In-vivo* Tests – Unpublished Studies

The antibacterial activity of salicylic acid tested *in-vivo* shows strong persistence of effect when tested for approximated use conditions using established test methods. Clinical evaluations demonstrated a significant log reduction of *E.coli* in rinse-off and non-rinse off formulations.

Health Care Personnel Handwash Test

Using ASTM method 1174, one rinse-off prototype containing 2% salicylic acid (SWH160-155), and one non-rinse off prototype containing 1% salicylic acid (SWH094-136) were tested vs. respective vehicle controls (Attachment VII). Results from this study are listed in Table 2. After one and ten washes, the rinse off product met minimum log reduction criteria proposed by the TFM for Healthcare Personnel Handwash products (59 FR 31401), and was statistically better than the vehicle control product (respective p-values =0.0010 and 0.0001). Due to the form of the leave-on product (wipe) it is believed that the mechanical action contributed to a high initial bacterial removal from both test product and vehicle, resulting in the absence of a significant difference in log reduction following one wash. However, after ten washes, reduction of bacteria following the use of the leave on with salicylic acid was one log higher, and statistically better (p=0.0044) than the vehicle control product, demonstrating that repeated use provides additional benefits over time. Results for two preliminary small base pilot studies conducted with these same formulations and test method are listed in Table 3. Reports and protocols for these studies are included in Appendix E.

Table 2 Summary of HCPHWT Log10 Bacterial Results

			Log10 Counts - 1 Wash			Log10 Counts - 10 Washes		
Treatment	Sample Size	Baseline Mean	Mean	Change from Baseline	Percent Reduction	Mean	Change from Baseline	Percent Reduction
1	16	6.71	3.91	**2.80**	99.84	3.79	**2.92**	99.88
2	16	6.81	3.52	**3.29**	99.95	3.00	**3.80**	99.98
3	16	6.66	4.22	**2.44**	99.64	3.48	**3.18**	99.93
4	16	6.63	4.34	**2.29**	99.49	4.19	**2.44**	99.64

Test Product 1 (SWH160-152) Vehicle control rinse-off, neutralized to pH 7 for consumer end use
Test Product 2 (SWH160-155) Rinse-off formulation containing 2% salicylic acid, pH 3
Test Product 3 (SWH094-136) Non rinse-off formulation containing 1% salicylic acid, pH3
Test Product 4 (SWH094-137) Vehicle control non-rinse off, neutralized to pH 7

Table 3 Summary of HCPHWT Log10 Bacterial Results (pilot studies)

			Log10 Counts - 1 Wash			Log10 Counts - 10 Washes		
Treatment	Sample Size	Baseline Mean	Mean	Change from Baseline	Percent Reduction	Mean	Change from Baseline	Percent Reduction
1	6	7.63	5.21	**2.42**	99.6	5.44	**2.19**	99.4
2	6	7.74	4.66	**3.09**	99.9	4.53	**3.21**	99.9

			Log10 Counts - 1 Wash			Log10 Counts - 10 Washes		
Treatment	Sample Size	Baseline Mean	Mean	Change from Baseline	Percent Reduction	Mean	Change from Baseline	Percent Reduction
3	4	7.43	5.54	**1.89**	98.7	4.05	**3.38**	>99.9
4	4	6.78	5.35	**1.43**	96.3	4.34	**2.44**	99.6

Residual Antibacterial Efficacy Test (RET) on forearms

Using a cylinder sampling test method (modified ASTM Test Method E1874-97) (47) the residual effectiveness of a rinse off product containing salicylic acid and varying levels of triclosan (TCS) was evaluated in a two part clinical study. The rinse off product was a commercially sold body wash (Olay Daily Renewal Body Wash) to which salicylic acid was added at levels of 0.5% and 1.0%. Part I investigated effects sixty minutes after inoculation under occluded conditions, and Part II investigated effects ten minutes after inoculation under occluded and unoccluded conditions. Both employed a single wash split forearm technique. Only the 1.0% salicylic acid product was tested in Part II. After sixty minutes, neither the 0.5% (no TCS) nor the 1.0% salicylic acid (no TCS) were statistically different from the vehicle control, however both were significantly more effective (p value = 0.10) at lowering levels of *E.coli* on the skin than the Ivory Liquid product, a marketed non-antibacterial handsoap product. Similarly, ten minutes after inoculation, the 1.0% salicylic acid product (no TCS) was not significantly better than the vehicle control, but was significantly better (p value = 0.10) than the Ivory Liquid product under both occluded and unoccluded conditions. In Part II of the study, product treatment and occlusion status were highly significant factors but their interaction and resulting pairwise p-values were not significant. Reports and protocols are included in Appendix F.

Antibacterial Efficacy *In-vitro* Tests – Unpublished Studies

The antibacterial activity of salicylic acid tested *in-vitro* shows a rapid rate of inactivation against standard strains of gram positive and gram negative bacteria when tested at time points typical of product use. Residual antibacterial effects of salicylic acid *in vitro* are evident in tests using pigskin substrate, and the results correlate well to clinical data which show residual benefits vs. non-antibacterial test products.

Time Kill Studies

Standard time kill solution assays were performed internally to determine the antibacterial efficacy of salicylic acid over time against a variety of gram positive and gram negative bacteria. Salicylic acid solutions were incubated with the microorganism (~10^8 cfu/mL) for either 30 seconds, one minute or five minutes, and aliquots were removed, neutralized and dilutions were made and immediately plated to determine titer levels. Microbial titers from salicylic samples were compared against a no treatment control. For each test, neutralization controls were also performed to ensure that the samples were effectively inactivated at the indicated timepoints.

Results demonstrated that within 30 seconds, **1% salicylic acid (dissolved in 20% ethanol)** killed all five organisms including: *P.aeruginosa, S.choleraesius, S.epidermis, E. coli, and S.aureus*. Maximum log reductions were observed at all timepoints in the 1% salicylic acid group. In contrast, the vehicle containing 20% ethanol (pH 7.0) was inactive against the five organisms at the 30 second and one minute timepoints. Only weak activity (1 log reduction) was seen against *S. aureus* and *S. epidermis* after a five minute exposure. Similarly, the placebo solution adjusted to pH 3 by HCl was also inactive at the 30 second and one minute timepoints, however this solution was weakly to strongly active against these organisms after five minutes exposure. These results indicate that salicylic acid is effective in solution and rapidly inactivates a wide variety of gram positive and gram negative microorganisms. Time Kill results for salicylic acid (simple solution, no formulation) are included in Attachment IX.

When 1% salicylic was formulated in **Test Product 3 (Attachment VII)** which is composed of a simple moisturizing base containing a humectant (pyrrolidone carboxylic acid (PCA)) and a surfactant (ammonium lauryl sulfide) (ALS)), the rapid and potent antibacterial activity was still retained, and maximal antimicrobial activities were observed for all organisms at all timepoints. In contrast, the placebo vehicle (containing PCA and ALS) was ineffective at inactivating *P. aeruginosa, S. cholerae* or

E. coli within five minutes. This base formulation was effective in inactivating *S. epidermis*, and *S. aureus*; these two organisms are known to be susceptible to anionic surfactants such as ALS. Thus, when dissociated at pH 3, salicylic acid delivers rapid and broad-spectrum antibacterial activity when formulated in this moisturizer base. This non-rinse formulation is identical to the one tested in HCPHW tests described above. Time kill results are included in Attachment IX.

Salicylic acid (2%) was next formulated in a typical hand-wash chassis (Test Product 2, Attachment VII). Again, this composition was maximally effective in inactivating all of the organisms tested within five minutes. In contrast, the placebo chassis delivered weak to moderate (1-2 log reduction) activity against *P. aeruginosa, E. coli*, and *S. aureus* within five minutes, and strong activity (> 3 log reduction) against *S. cholerae* and *S. epidermis*. Thus, when dissociated at pH 3, the addition of 2% salicylic acid delivered broad-spectrum activity in a wash formulation and improved the antimicrobial activity of this chassis. This rinse off formulation is identical to the one tested in HCPHW tests described above. Time kill results for this formulation are included in Attachment IX.

Residual Antibacterial Efficacy using Pigskin Substrate

Residual efficacy testing using pigskin for a substrate was performed to determine skin or surface residual activity by salicylic acid. In this test, a 5 cm^2 pigskin disc (n=6) was inoculated with 50 µL of the product solution. A dry time of 15 minutes is allotted before the substrate is inoculated with 6.25 µL of the test organism, *E. coli* 11229, and extracted either one or ten minutes later.

As shown in the table below, 1% salicylic acid (solubilized in 1% ammonium lauryl sulfate (ALS)) effectively delivered antibacterial efficacy on a pigskin surface within one minute and retained this activity over a 10 minute time period. In contrast, ALS was not active in this test. This demonstrates that 1% salicylic acid provides significant residual antibacterial efficacy on a skin substrate (48).

Table 4 Residual Efficacy (Log Reduction vs. Control)

Test Material	pH	1 min	10 min
1% Salicylic acid, 1% ALS	3.0	2.1	2.0
1% ALS	3.0	0.1	0.2

PRACTICAL ADVANTAGE FOR CONSUMER PRODUCTS

Salicylic acid will provide Industry greater flexibility for formulating safe and effective topical antimicrobial products that are used repetitively by household consumers, food handler personnel, and health care personnel on a daily basis.

Statistics show that consumers want the option to buy skin cleansers with antibacterial activity. During a 52 week period ending April 15, 2001 there were approximately 17.2 million antibacterial personal care products sold in the United States, and during the calendar year 2000, the U.S. sales volume for topical antibacterial cleansing products totaled 570 million dollars (49). Only two ingredients, povidone iodine 5-10%, and alcohol, 60-95%, are currently included in the TFM as Category I active ingredients for use in antiseptic or health care personnel handwashes. Although these ingredients are safe and effective antimicrobial agents, they are often practical limitations for formulating in consumer based products intended for daily, repetitive use in household or health care settings (e.g., staining of iodine on the skin and lack of substantive effect as with alcohol). Inclusion of salicylic acid as an approved antibacterial Category I ingredient would result in an appropriate benefit to risk by providing the consumer with the antibacterial benefits they desire, while providing Industry with more flexibility for formulating products that are safe, efficacious and consumer acceptable.

CONCLUSION

As presented in this petition, it is believed there are sufficient grounds to find salicylic as a Category I antibacterial active ingredient for use in consumer hand products, food handler products and health care personnel hand products. Salicylic acid has a long history of safe and effective marketing prior to the establishment of the OTC Drug Review process, and subsequently as a monograph drug in products used daily and/or repeatedly on the skin for treatment of acne, dandruff, seborrheic dermatitis, psoriasis, corns, calluses and warts. In other parts of the world, it is approved for use as an active ingredient for these same indications, and as an antimicrobial active ingredient in antiseptic skin cleansers sold in mass markets. Salicylic acid is also included as an ingredient in cosmetics sold on a broad scale both in the U.S. and abroad, and in addition to its topical use in personal care products, it is included in human prescription and veterinary drugs. In total, it is included in approximately nine hundred different products sold in over sixty-six countries (50).

As part of the U.S. monograph process, safety data have been reviewed by expert panels that concluded salicylic acid is safe for intended use at usage levels comparable to those proposed for antimicrobial use in skin cleansers. Additionally, based on scientific literature and human safety data, a recently published Cosmetic Ingredient Review (CIR) found salicylic acid to be safe in cosmetics when formulated or labeled to avoid irritation and sun sensitivity. Although salicylates have been associated with salicylism, reproductive toxicity and Reyes Syndrome, internally prepared risk assessments have determined that there is no anticipated safety risk expected with the use of salicylic acid as proposed, based on proposed usage levels, product form and anticipated exposure. Based on recommendations included in these assessments, an applicable label warning statement for children under the age of twelve months is proposed for leave-on antimicrobial cleansers containing salicylic acid.

The antibacterial efficacy of salicylic acid has been demonstrated in studies found in published literature, and in internal tests using ASTM and/or published methods. Salicylic acid has a rapid rate of inactivation against a wide range of organisms, and as demonstrated in HCPHW tests, has a strong persistence of effect, and significantly greater bacterial log reductions vs. a non-active vehicle control.

C. Environmental Impact

The Procter & Gamble Company citing 21CFR §25.31(b) claims a categorical exclusion from submitting an environmental assessment in support of this petition. As a result of the requested action to amend the Tentative Final Monograph for Health Care Antiseptic Drug Products for Over-the-Counter Use, the estimated environmental concentration of salicylic acid will be below 1 ppb. Further, there are no data to suggest that at the expected level of exposure, salicylic acid may be toxic to organisms in the environment. There is no evidence that any extraordinary circumstances exist.

D. Economic Impact

This will be provided upon request from the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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The Procter & Gamble Company
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Cincinnati, Ohio 45241
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Attachments

I. Label Templates

II(a) Exposure and risk assessment for the first signs of salicylicism in a child using a non-rinse antibacterial product with salicylic acid

II(b) Exposure and risk assessment for the first signs of salicylicism in a child using a rinse-off antibacterial product with salicylic acid

III(a) Exposure and risk assessment for the reproductive toxicity in an adult female using a non-rinse antibacterial product with salicylic acid

III(b) Exposure and risk assessment for the reproductive toxicity in an adult female using a rinse-off antibacterial product with salicylic acid

IV. Suspected Causes of Reyes Syndrome

V(a) Exposure and risk assessment for non-rinse antibacterial products with salicylic acid where the endpoint of concern is the lowest systemic load of salicylate associated with Reyes Syndrome

V(b) Exposure and risk assessment for rinse-off antibacterial products with salicylic acid where the endpoint of concern is the lowest systemic load of salicylate associated with Reyes Syndrome

VI. Adverse Events Summary

VII. Test Product Formulations/ Analytical assays and validation of method

VIII. Minimum Inhibitory Concentration (MIC) Tables

IX. Time Kill Results

X. Pharmacology of Salicylic Acid

Appendices

A. Human Safety dossier submitted to the European Union SCC
B. OTC Drug Panel Reviews of Salicylic Acid for Treatment of Topical Conditions
C. CTFA's Cosmetic Ingredient Review (CIR) Final Report on Salicylic Acid
D. Post Market Surveillance Reports of Adverse Effects for Topical Products with Salicylic Acid
E. Protocol and Final Report for Health Care Personnel Handwash Studies
F. Protocol and Final Report for Antibacterial Residual Efficacy Studies
G. Published Literature References

References:

1. Needs J and Brooks PM (1985) "Clinical Pharmacokinetics of the Salicylates" *Clinical Pharmacokinetics* 10: 164-167.

2. Clissold SP (1986) "Aspirin and Related Derivatives of Salicylic Acid" *Drugs* 32 (Suppl 4): 8-26.

3. Taylor JR and Halprin KM (1975) "Percutaneous absorption of salicylic acid" *Arch Dermatol* 111: 740-743.

4. Gilman AG, Rall TW, Nies AS and Taylor P. (1990) Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eighth edition. Pergamon Press New York, 644-654.

5. Lewis RB and Schulman JD (1973) "Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis , on the duration of human gestation and labor" *Lancet* 1: 1159-61.

6. Collins E and Turner G (1975) "Fetal effects of regular salicylate ingestion in pregnancy" *Lancet* 2: 338-339).

7. Dekker GA and Sibai BM (1993) "Low dose aspirin in the prevention of preclampsia and fetal growth retardation: Rationale, mechanisms and clinical trials" *Am J Obstet Gynecol* 168: 214-227.

8. Goldsmith L (1979) "Salicylic acid" *Int. J Dermatol* 18: 32-6.

9. Birmingham BK, Greene DS and Rhodes CT (1979) "Percutaneous absorption of salicylic acid in rabbits" *Drug Dev Indust Pharm* 5: 29-40.

10. Taylor JR and Halprin KM (1975) "Percutaneous absorption of salicylic acid" *Arch Dermatol* 111: 740-743.

11. Davis DP (1997) *J. Pharm Sci* 86: 896-899

12. Reye RDK, Morgan G and Baral J (1963) "Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood." *Lancet* 2: 749.

13. Johnson GM, Scurletis TD and Carroll NB (1963). "A study of sixteen fatal cases of encephalitis-like diseases in North Carolina children" *NC Med J* 24: 464.

14. Heubi JE, Partin JC, Partin JS and Schubert WK (1987) "Reye's syndrome: current concepts. *Hepatology* 7: 155-64.

15. DeVivo DC (1985) "Reye syndrome" *Neurol Clin* 3: 95.

16. Trauner DA (1982) "Reye Syndrome" *Curr Probl Pediatr* 12(1): 23-4.

17. Brown RE and Forman DT (1982) "The biochemistry of Reye's syndrome" *CRC Crit Rev Clin Lab Sci* 17: 247.

18. Hurwitz ES and Goodman RA (1982) "A cluster of cases of Reye's syndrome associated with chickenpox" *Pediatrics* 70: 901-06.

19. Hall S and Bellman M (1984) "Reye's syndrome in the British Isles" *BMJ* 288: 548-50.

20. Brown JK and Imam H (1991) "Interrelationship of liver and brain with special reference to Reye syndrome" *J Inher Metab Dis* 14(4): 436-58.

21. Visentin M, Slmona M and Tacconi MT (1995) "Reye's and Reye-like syndromes, drug related diseases?" *Drug Metab Rev* 27(3): 517-39.

22. Feinman SE (1994) Beneficial and Toxic Effects of Aspirin CRC Press London 89-95

23. Rainsford KD, Schwietzer A and Brune K (1993) "Distribution of the acetyl compared with the salicyl moiety of acetylsalicylic acid" *Biochem Pharm* 32: 1301-08.

24. Mortimer EA and Lepow ML (1962) "Varicella with hypoglycemia Possibly due to Salicylates" *American Journal of Diseases of Children* 103: 91-98.

25. Snodgrass WR (1986) "Salicylate Toxicity" *Pediatric Clinics of North America* 33(2): 381-391.

26. Partin JS, Schubert WK, Partin JC and Hammond JG (1982) "Serum salicylate concentrations in Reye's disease" *Lancet* 1: 191.

27. Starko KM, Ray CG, Diminguez LB, Stromberg WL and Woodall DF (1980) "Reye's syndrome and salicylate use" *Pediatrics* 66: 859-64.

28. Waldman RJ, Hall WN, McGee H and VanAmburg G (1982) "Aspirin as a risk factor in Reye's syndrome" *JAMA* 247: 3089-3094.

29. Halpin TJ, Holtzhauer FJ, Campbell RJ, Hall LJ, Correa-Villasenor A, Lanese R, Rice J and Hurwitz ES (1982) "Reye's syndrome and medication use" *JAMA* 248 (6) 687-91.

30. Hurwitz ES, Barrett MJ, Bregman D, Gunn WJ, Pinsky P, Schonberger LB, Drage JS, Kaslow RA, Burlington DB, Quinnan GV, LaMontagne JR, Fairweather WR, Dayton D and Dowdle WR (1987) "Public Health Service study of Reye's syndrome and medications" *JAMA* 257(14): 1905-11.

31. Forsyth BW, Horwitz RI, Acampora D, Shapiro ED, Viscoli CM, Feinstein AR, Henner R, Holabird NB, Jones BA, Karabelas AD, Kramer MS, Miclette M, Wells JA (1989) "New Epidemiologic Evidence Confirming That Bias Does Not Explin the Aspirin/Reye's Syndrome Association" *JAMA* 261(17): 2517-2524.

32. Hall SM, Plaster PA, Glasgow JFT, Hancock P (1988) "Preadmission antipyretics in Reye's Syndrome" *Archives of Disease in Childhood* 63: 857-866.

33. Chu AB, Nerurkar LS, Witzel N, Andresen BD, Alexander M, Kang ES, Brouwers P, Fedio P, Lee YJ, Server JL (1986) "Reye's syndrome: salicylate metabolism, viral antibody levels, and other factors in surviving patients and unaffected family members" *Amer J Dis Child* 140: 1009.

34. Kang ES, Crocker JFS, and Johnson GM (1986) "Letter to the editor" *N Engl J Med* 314: 920.

35. Hurwitz ES (1989) "Reyes Syndrome" *Epidemiol Rev* 11: 249

36. Orlowski JP, Gillis J and Kilham HA (1987) "A Catch in the Reye" *Pediatrics* 80(5): 638-42.

37. Orlowski JP, CampbellP and Goldstein S (1990) "Reye's syndrome: a case control study of medication use and associated viruses in Australia" *Cleveland Clin J Med* 57(4): 323-9.

38. Biometric Research Institute (1986) "Analysis of Exposure to non-aspirin salicylates among subjects from the Ohio Dept of Health Survey and the Public Health Service Pilot Study on Reyes Syndrom". June Report.

39. Cosmetic and Drug Preservation Principles and Practices; Kabara, Jon J., editor; Marcel Dekker, Inc.; New York and Basel; pp 672-673

40. Kirk-Othmer Encyclopedia of Chemical Technology; Disinfectants and Antiseptics, Volume 8, Fourth Edition; 1991; pp 251- 253

41. Scherrer, M.; Knusel F; et. al.; "Antimicrobial activity of broad spectrum antimicrobial agents, with special reference to salicylic acid"; Mykosen; Vol 7 (6); July 1, 1971; pp 323-234

42. Hartmann, AA; "Influence of various factors on the human resident skin flora"; Seminars in Dermatology; Vol 9, No. 4; 1990; pp 305-308

43. Muller, E., et.al.; "Mechanism of salicylate-mediated inhibition of biofilm in Staphyloccous epidermis"; Journal of Infectious Diseases; Vol. 177, No. 2; 1998; pp 501-503

44. Price, Christopher, et.al; "The Effects of Salicylates on Bacteria"; International Journal of Biochemistry and Cell Biology; Vol 32 10) pp 1029-1043; Oct. 2000

45. Esposito, S. et. al.; "Effect of salicylates on antibiotic activity" J. Chemotherapy (2) 1990; pp 87-90

46. Eady, E. Anne; "Antibiotic resistance and skin bacteria: current trends and future prospects. Relevance to acne therapy"; Acne and Related Disorders; Marks, R. and Plewig, G., editors; Dunitz, London, 1989; pp127-131

47. Williamson, P. and Kligman, A.M.; "A method for the quantitative investigation of cutaneous bacteria"; J. Invest Dermatology; 45:6; 1965; pp 498-503

48. Procter & Gamble unpublished test results

49. Information Resources, Inc. (IRI); 150 North Clinton Street, Chicago, Illinois, 60661, May, 2001

50. Chemical Information Services, Worldwide Bulk Drug Users Directory Database; 9550 Forest Lane Suite 321, Dallas, TX 75243; March, 2001

Attachment I

Proposed antibacterial labeling for HEALTHCARE PERSONNEL HAND PRODUCT

Statement of identity:
'Antibacterial' or 'antiseptic' followed by statement of classification of product form e.g. 'foam', 'gel', 'liquid' etc. and/or product type e.g. 'wash', 'sanitizer', 'rinse', 'scrub' etc., or other appropriate topical product forms or types.

Other truthful and non-misleading statements describing the product category should be optional e.g. 'healthcare personnel hand sanitizer', 'healthcare professional hand wash', 'healthcare personnel hand rinse' etc.

Indications:
'Decreases' / 'kills' / 'reduces' / 'eliminates' (followed by) 'bacteria' (followed by) 'on the hands'.

'Decreases' / 'kills' / 'reduces' / 'eliminates' (followed by) 'bacteria that potentially can cause' (followed by) 'disease' or 'infection'.

'Helps' (followed by) 'prevent' or 'reduce' (followed by) 'the transfer' or 'the transmission' or 'the spread' or 'the cross-contamination' (followed by) 'of bacteria'.

'Helps prevent' or 'inhibits' (followed by) 'the growth of' or 'the regrowth of' (followed by) 'bacteria' (followed by) 'on the hands'.

Directions for use:
The directions described below are illustrative for products that are intended to remain on the skin, or be removed from the skin after application. These directions should be amended appropriately to describe the specific topical product dosage form &/or product type being used.

- Water Use (before applying product and rinsing): 'Wet arms, (optionally) forearms or other body sites. Apply' (quantity of product) 'to hands, (optionally) forearms or other body sites'. (Select) 'Wash or scrub thoroughly for' (insert duration). 'Rinse thoroughly'. (Insert applicable directions for repeat washing).

- Water Use (rinse only after using product): 'Apply' (quantity of product) 'to hands, (optionally) forearms or other body sites'. Select 'Wash or scrub thoroughly for' (insert duration). 'Rinse thoroughly'. (Insert applicable directions for repeat washing).

- No Water Necessary: 'Apply' (quantity of product) 'to hands, (optionally) forearms or other body sites. Spread on both hands, (optionally) forearms or other body sites. Rub thoroughly for' (insert duration) or 'until dry'. (Insert other directions as needed.)

Warnings:

- Products must comply with the appropriate sections of 21 CFR 201 and 21 CFR 330.
- 'Discontinue use if irritation or redness develop. If condition persists, consult a doctor'.
- For leave-on salicylic acid containing formulations: Do not use this product on children under twelve months of age. For use on hands only.

Attachment I

Proposed antibacterial labeling for FOOD HANDLER PRODUCT

Statement of identity: 'Antibacterial' or 'antiseptic' followed by statement of classification of product form e.g. 'foam', 'gel', 'liquid' etc. and/or product type e.g. 'wash', 'sanitizer', 'rinse', 'dip' etc., or other appropriate topical product forms or types. Other truthful and non-misleading statements describing the product category should be optional e.g. 'food handler hand sanitizer', 'food handler hand dip', 'food handler wash' etc.
Indications: 'Decreases' / 'kills' / 'reduces' / 'eliminates' (followed by) 'bacteria' (followed by) 'on the hands' (followed by, if desired) 'before and after handling food'. 'Decreases' / 'kills' / 'reduces'/ 'eliminates' (followed by) 'bacteria on the hands that potentially can cause' (followed by) 'disease' or 'foodborne disease' or 'foodborne illness'. 'Helps' (followed by) 'prevent' or 'reduce' (followed by) 'the transfer' or 'the transmission' or 'the spread' or 'the cross-contamination' (followed by) 'of bacteria'.
Directions for use: Provide usage directions consistent with the product form.
Warnings: • Products must comply with the appropriate sections of 21 CFR 201 and 21 CFR 330. • 'Discontinue use if irritation or redness develop. If condition persists, consult a doctor'. • For leave-on salicylic acid containing formulations: Do not use this product on children under twelve months of age. For use on hands only.

Attachment I

Proposed antibacterial labeling for CONSUMER HAND PRODUCT

Statement of identity: 'Antibacterial' followed by statement of classification of product form e.g. 'foam', 'bar', 'gel', 'liquid' etc. and/or product type e.g. 'wash', 'sanitizer', 'rinse', 'soap' etc., or other appropriate topical product forms or types. Other truthful and non-misleading statements describing the product category should be optional e.g. 'antibacterial hand soap', 'antibacterial hand gel', 'antibacterial hand towelette' etc.
Indications: 'Decreases' / 'kills' / 'reduces' / 'eliminates' (followed by) 'bacteria' (followed by) 'on the hands' (followed by, if desired) 'after changing diapers / attending day care / caring for (sick or elderly or invalid) family members, individuals or people'. 'Helps' (followed by) 'prevent' or 'reduce' (followed by) 'the transfer' or 'the transmission' or 'the spread' (followed by) 'of bacteria on the hands'. 'Helps prevent' or 'inhibits' (followed by) 'the growth of' or 'the regrowth of' (followed by) 'bacteria' (followed by) 'on the hands'.
Directions for use: Due to customary conditions of use, directions for use may not be required. Non-customary topical dosage forms or delivery systems should include directions which reflect the conditions used when the product was tested.
Warnings: • Products must comply with the appropriate sections of 21 CFR 201 and 21 CFR 330. • 'Keep out of the reach of children except under adult supervision. If swallowed, get medical help or contact a Poison Control Center right away'. • No category warnings are required. Individual warning statements may be required for specific ingredients. • For leave-on salicylic acid containing formulations: Do not use this product on children under twelve months of age. For use on hands only.

Attachment IIa

Exposure and Risk Assessment for the First Signs of Salicylicism in a Child using a Non-rinse Antibacterial Product containing SA

Assumptions for non-rinse (n.r.) application:

- Average Body Weight of a 1 year old child (50th percentile from Center for Disease Control Growth Charts) = 10kg
- Amount of product used per application = 1.0 grams
- Maximum amount of SA= 1.2%
- Amount of SA deposited = 100%
- Amount of SA absorbed (based on reference Davis et al., 1997[1])= 44%
- Amount of blood in a typical adult (based on previous FDA SA monographs)= 7 liters
- Amount of blood in a typical 1 year old (based on Reference Man[2] formula: 82.7x BW (in kg)-25)/1000 = 0.80 liters
- Effect level for first signs of salicylicism (based on previous FDA SA monographs) = 12.2 mg/100 ml blood

Exposure Assessment Calculations for non-rinse (n.r.) product used in a 1-year old child:

$$\frac{(1\text{ g n.r. product})(1.2\text{ g Sal acid})\ (100\%\text{ deposition})(44\%\text{ absorption})(1000\text{ mg})}{(\text{person})\qquad(100\text{ g n.r. product})\qquad\qquad(0.80\text{ L blood volume})\ (\text{g})} = 6.6\text{ mg SA/L blood}$$

Since $\frac{(6.6\text{ mg})(1\text{ L blood})}{(\text{L blood})(1000\text{ ml})} = 0.0066$ mg/ml, which means that there would be **0.66 mg SA/100 mls blood**

Risk Assessment Calculations for non-rinse product used in a 1-year old child:

$$\text{C.}\quad \frac{\textbf{Effect level for salicylicism}}{\text{Predicted blood level for child using n.r. product}} = \frac{\textbf{12.2 mg/100ml blood}}{0.66\text{ mg/100 ml blood}} = \textbf{18.5x margin of safety}$$

Conclusion for non rinse applications: Although the FDA has used 30 – 50 mg/100mls blood as a benchmark for salicylicism in previous monographs, 12.2 mg/100 mls has been identified in these same monographs as the effect level for first signs of salicylicism. Since children could potentially use a SA containing antibacterial product, this lower number was used for conservatism. The predicted blood level following a one time use of a leave-on SA containing antibacterial product would be anticipated to result in a blood level of 0.66 mg/100 mls blood. This blood level is 24 fold below the effect level benchmark. If a child were to use such a product even ten times per day, the blood level would still remain below this effect level. Since the half life of SA is relatively short 2-3 hours, even this excessive use of product would not be expected to pose a safety risk. Since the blood volume of an adult is much larger than a child no safety risk is anticipated for adult use (estimated blood levels would be approximately 0.07 mg SA/ 100 mls blood for an adult with a 7L blood volume).

[1]Davis DP (1997) *J. Pharm Sci* 86: 896-899.

[2]International Commission on Radiological Protection (1974) Report of the Tast Group on Reference Man, Pergamon Press, NY p 33.

Attachment IIb

Exposure and Risk Assessment for the First Signs of Salicylicism in a Child using a Rinse-off Antibacterial Product Containing Salicylic Acid

Assumptions for rinsed application:

- Average Body Weight of a 1 year old child (50th percentile from Center for Disease Control Growth Charts) = 10 kg
- Amount of product used per application (accounts for misuse as body wash or multiple handwash use scenarios) = 10 grams
- Maximum amount of SA= 3.5%
- Amount of SA deposited (due to rinse off nature) = 1%
- Amount of SA absorbed (based on reference Davis et al., 1997 plus some additional accounting for potential of surfactants to increase penetration)= 50%
- Amount of blood in a typical adult (based on previous FDA SA monographs)= 7 litres
- Amount of blood in a typical 1 year old (based on Reference Man[1] formula: 82.7x BW (in kg)-25)/1000 = 0.80 litres
- Effect level for first signs of salicylicism (based on previous FDA SA monographs) = 12.2 mg/100 ml blood

Exposure Assessment Calculations for rinsed product used in a 1-year old child:

$$\frac{(10\text{ g rinsed. product})(3.0\text{ g Sal acid})(1\%\text{ deposition})(50\%\text{ absorption})(1000\text{ mg})}{(\text{person})\qquad(100\text{ g rinsed product})\qquad(0.80\text{ L blood volume})\ (\text{g})} = 1.9\text{ mg SA/L blood}$$

Since $\frac{(1.9\text{ mg})(1\text{ L blood})}{(\text{L blood})(1000\text{ ml})} = 0.0019$ mg/ml, which means that there would be **0.19 mg SA/100 mls blood**

Risk Assessment Calculations for rinsed product used in a 1-year old child:

D. $\frac{\text{Effect level for salicylicism}}{\text{Blood level for child using rinsed product}} = \frac{\textbf{12.2 mg/100ml blood}}{0.19\text{ mg/100 ml blood}} = \textbf{64x margin of safety}$

Conclusion for rinsed applications: Although the FDA has used 30 – 50 mg/100mls blood as a benchmark for salicylicism in previous monographs, 12.2 mg/100 mls has been identified in these same monographs as the effect level for first signs of salicylicism. Since children could potentially use a SA containing antibacterial product this lower number was used for conservatism. The predicted blood level following a one-time use of 10 grams of a rinse off product containing SA would be anticipated to result in a blood level of 0.19 mg/100 mls blood. This blood level is 64 fold below the effect level benchmark. A 10 gram per day scenario suggests numerous hand washes or a misuse as bodywash application. Even an excessive use of such a rinse off product (particularly since the half life of SA is relatively short 2-3 hours) would not be expected to pose a safety risk. Since the blood volume of an adult is much larger than a child no safety risk is anticipated for adult use (estimated blood levels would be approximately 0.02 mg SA/ 100 mls blood for an adult with a 7L blood volume).

[1]International Commission on Radiological Protection (1974) Report of the Tast Group on Reference Man, Pergamon Press, NY p 33.

Attachment IIIa

Exposure and Risk Assessment for Reproductive Toxicity in an Adult Female using a Non-rinse Antibacterial Product Containing Salicylic acid

Assumptions for non-rinse (n.r.) application:

- Average Body Weight of an adult female =58 kg
- Amount of product used per application = 1.0 grams
- Maximum amount of SA= 1.2%
- Amount of SA deposited = 100%
- Amount of SA absorbed (based on reference Davis et al., 1997)= 44%
- Amount of SA equivalent to ingestion of one baby aspirin* = 62 mg
- Systemic load of SA in 58 kg person after ingestion of one baby aspirin = 62 mg/58kg =1.07 mg/kg/d

* level identified by Teratogen information Sevice Database as a safe amount of SA for adult pregnant women (see text for more detail on this database)

Exposure Assessment Calculations for non-rinse (n.r.) product used in a pregnant female:

$$\frac{(1\text{ g n.r. product})(1.2\text{ g Sal acid})\,(100\%\text{ deposition})(44\%\text{ absorption})(1000\text{ mg})}{(58\text{ kg person})(100\text{ g n.r. product})\qquad\qquad(\text{g})} = 0.09\text{ mg SA/kg}$$

Risk Assessment Calculations for non-rinse product used in an adult female:

E. $\frac{\text{Safe systemic load of SA in a pregnant female}}{\text{Predicted systemic load after use of n.r. product}}$ **=** $\frac{\text{1.07 mg/kg/d}}{0.09\text{ mg/kg/d}}$ **= 12x margin of safety**

Conclusion: The ingestion of one baby aspirin per day is considered a safe level of acetylsalicylic acid (ASA) for an adult pregnant women (Teratogen Information Service Database). Since one baby aspirin contains 81 mg of ASA, the corresponding amount of SA expected to be formed in the stomach would be 62 mg or about 76% of parent compound. If 62 mg of SA were in the blood of an adult pregnant female weighing 58 kg, the systemic load would be 1.07 mg/kg/d. An adult pregnant female using a non rinse antibacterial product containing up to 1.2% SA would be anticipated to have a systemic load of 0.09 mg/kg/d. Thus the systemic load from the antibacterial product would be less then that resulting from ingestion of one baby aspirin. Even up to 10 uses of antibacterial product containing 1.2% SA would not be expected to result in any risk to mother or baby. Additionally, in a multiple use scenario, since the half-life of SA is relatively short (2-3 hours), even this excessive use of product would not be expected to pose a safety risk.

Attachment IIIb

Exposure and Risk Assessment for Reproductive Toxicity in an Adult Female using a Rinse-off Antibacterial Product Containing Salicylic Acid

Assumptions for rinsed application:

- Average Body Weight of an adult female =58 kg
- Amount of product used per application (accounts for misuse as body wash or multiple handwash use scenarios) = 10 grams
- Maximum amount of SA= 3.5%
- Amount of SA deposited (due to rinse off nature) = 1%
- Amount of SA absorbed (based on reference Davis et al., 1997 plus some additional accounting for potential of surfactants to increase penetration)= 50%
- Amount of SA equivalent to ingestion of one baby aspirin* = 62 mg
- Systemic load of SA in 58 kg person after ingestion of one baby aspirin = 62 mg/58kg =1.07 mg/kg/d

* level identified by Teratogen information Sevice Database as a safe amount of SA for adult pregnant women (see text for more detail on this database)

Exposure Assessment Calculations for rinse-off product used in a pregnant female:

$$\frac{(10\text{ g . product})(3.5\text{ g Sal acid})\,(1\%\text{ deposition})(50\%\text{ absorption})(1000\text{ mg})}{(58\text{ kg person})(100\text{ g. product})\qquad\qquad(\text{g})} = 0.03\text{ mg SA/kg}$$

Risk Assessment Calculations for non-rinse product used in an adult female:

F. **Safe systemic load of SA in a pregnant female** **= 1.07 mg/kg/d = 35.7x margin of safety**
Predicted systemic load after use of rinsed product 0.03 mg/kg/d

Conclusion: Using the same rationale as above, the ingestion of one baby aspirin per day by a pregnant female (1.07 mg/kg/d) was used as a benchmark for no risk to mother or baby. An adult pregnant female using a rinsed antibacterial product containing up to 3.5% SA would be anticipated to have a systemic load of 0.03 mg/kg/d. Thus the systemic load from the antibacterial product would be less then that resulting from ingestion of one baby aspirin. Even up to 10 uses of antibacterial product containing 3.5% SA would not be expected to result in any risk to mother or baby. Additionally, in a multiple use scenario, since the half-life of SA is relatively short (2-3 hours), even this excessive use of product would not be expected to pose a safety risk.

Attachment IV

Table I: Suspected Causes of Reyes Syndrome

((Brown and Imam, 1991; Visentin et al, 1995; Casteels-VanDaele, 1991)

Infection:

Influenza A
Influenza B

Parinfulenza
Adenovirus
Coxsackie
Cytomegalovirus
Herpes Simplex

Toxic:

Aspirin
Sodium valproate
Aflatoxin
Hypoglycine
Insecticides
Bacterial Endotoxin

Inborn Errors of Metabolism:

Ornithine transcarbamylase deficiency
Carbamyl phosphate synthetase deficiency
Pyruvate carboxylase deficiency
Varicella zoster
Glutaric aciduria type II
Biotinidase deficiency
Carnitine deficiency
Isovaleric academia
Carnitine palmitoyl transferase deficiency
3-hydroxyl, 3-methylglutaryl-CoA lyase deficiency
Medium and Long chain acyl-Co-A dehydrogenase deficience
Late onset citrullinaemia

Hypoxia

Status epilepticus

Attachment Va

Exposure and Risk Assessment for Non-rinse Antibacterial Products containing Salicylic Acid where the Endpoint of Concern is the Lowest Systemic Load of Salicylate that has been Associated with Reyes syndrome

Assumptions for non-rinse (n.r.) application:

- Average Body Weight of a 1 year old child (50th percentile from the Center for Disease Control Growth Charts) = 10 kg
- Amount of product used per application = 1.0 grams
- Maximum amount of SA= 1.2%
- Amount of SA deposited = 100%
- Lowest salicylate systemic load blood level that could be associated with Reyes (based on smallest oral dose available i.e., one baby aspirin; Hurwitz et al., 1987)
  = 62 mg SA/ 15 kg = 4.13 mg/kg

Exposure Assessment Calculations for non-rinse (n.r.) product used in a 1-year old child:

$$\frac{(1\text{ g n.r. product})(1.2\text{ g Sal acid})\ (100\%\text{ deposition})(44\%\text{ absorption})(1000\text{ mg})}{(10\text{ kg})\qquad(100\text{ g n.r. product})\qquad(\text{g})} = 0.53\text{ mg SA/kg}$$

Risk Assessment Calculations for non-rinse product used in a 1-year old child:

G. $\frac{\text{Systemic load of SA following ingestion of one baby aspirin}}{\text{Predicted systemic load for child using n.r. product}} = \frac{\text{4.13 mg/kg}}{\text{0.53 mg/kg}} =$ **7.7x**

Conclusion: One baby aspirin was the lowest concentration of ASA reported as ingested and found to possibly be associated with Reyes in the report of the US Public Health Service (USPHS) Study of Reye's Syndrome and Medications (Hurwitz et al., 1987). The concentration of one baby aspirin is known to be 81 mg ASA that is hydrolyzed in the stomach to 62 mg SA. If the body weight of a 1-year old child is considered in relation to the 62 mg SA ingested, the systemic load is estimated to be 4.13 mg/kg. When this value (4.13 mg/kg) is compared to the estimated systemic load from one use of a non-rinse SA containing antibacterial product (0.53 mg/kg) a 7.7 x difference in systemic loads is indicated. It would follow that up to 10 daily uses of such an antibacterial product on a 1-year old child could lead to systemic loads of SA which are equal to or slightly greater than the value for ingestion of one baby aspirin. The risk associated with this systemic load is put in perspective when the following statements are considered. The USPHS concluded that "Analysis of the independent risk of ASA and non-acetylsalicylic acid (NASA) salicylates revealed a significant association with ASA; the independent risk of NASA salicylates could not be assessed because only two cases were not exposed to ASA". The FDA, following its review of available data, issued a rule on June 9, 1988 to extend its requirement for Reyes labeling of oral and rectal ASA and ASA-containing products (21 CFR 201.314). In concluding that RS labeling should not be extended to NASA salicylates, the FDA stated in part, "FDA notes that the scientific research to date (1988) on which the Reyes warning statement requirement is based, focuses on the association between Reyes and ASA, rather than on the broader category of drug products containing Non-acetylsalicylic acid salicylates. Indeed, the USPHS study reported that there were too few subjects with reported exposures to non-acetylsalicylic acid salicylates.for a meaningful analysis." These statements and many other studies support the belief that NASA salicylates are not associated with Reyes (31, 37,38). For these reasons, it is arguable that children exposed to an antibacterial non-rinse application would be anticipated to be at no risk of enhanced likelihood of developing Reyes Syndrome and thus no label suggesting avoidance of the product when experiencing flu like conditions is recommended.

Attachment Vb

Exposure and Risk Assessment for Rinse-off Antibacterial Products Containing Salicylic Acid where the Endpoint of Concern is the Lowest Systemic Load of Salicylate that has been Associated with Reyes Syndrome

Assumptions for rinsed application:

- Average Body Weight of a 1 year old child (50th percentile from CDC Growth Charts)= 10 kg
- Amount of product used per application (accounts for misuse as body wash or multiple handwash use scenarios) = 10 grams
- Amount of SA deposited (due to rinse off nature) = 1%
- Amount of SA absorbed (based on reference Davis et al., 1997 plus some additional accounting for potential of surfactants to increase penetration)= 50%
- Maximum amount of SA= 3.5%
- Lowest salicylate systemic load blood level that could be associated with Reyes (based on smallest oral dose available i.e., one baby aspirin/ Body weight of a 3 year old child; Hurwitz et al., 1987) = 62 mg SA/ 15 kg = 4.13 mg/kg

Exposure Assessment Calculations for rinse-off product used in a 1-year old child:

$$\frac{(10\text{ g . product})(3.5\text{ g Sal acid})\ (1\%\text{ deposition})(50\%\text{ absorption})(1000\text{ mg})}{(10\text{ kg person})(100\text{ g. product})(\text{g})} = 0.18\text{ mg SA/kg}$$

Risk Assessment Calculations for rinse-off product used in a 1-year old child:

H. **Systemic load of SA following ingestion of one baby aspirin = 4.13 mg/kg = 23x**
Predicted systemic load for child using rinse-off product 0.18 mg/kg

Conclusion: See above rationale for why no warning label is suggested.

Attachment VI

Reported Post Market Adverse Events for Topical Products Containing Salicylic Acid

The adverse events associated with topically applied products containing salicylic acid included in this summary are being evaluated for frequency of reporting only, and are not being interpreted with certainty as having a cause and effect relationship with the drug. (1) (2).

FDA Spontaneous Reporting System (1969–1997)

According to FDA's Spontaneous Reporting System maintained by the Division of Epidemiology and Surveillance, there were nineteen reported adverse events for topically applied products containing salicylic acid sold in the U.S. during the period from 1969 – November 1, 1997. Based on the source of the reports, salicylic acid was considered suspect for its association with the cause of fifteen of these incidents involving seven individuals. The source of the reports included either a health care professional, or the individual consumer of the product.

The clinical description of each of the fifteen incidents included one or more localized, dermatological response(s) at the site of application. With the exception of one case of dermatitis, all responses occurred on the first day of use. These included:

- One 17 year old female experienced contact dermatitis
- One (age not reported) female experienced contact dermatitis after four days of daily application
- One 13 year old female experienced generalized application site reaction, pain and skin discoloration
- One 14 year old female experienced exfoliated dermatitis, edema and skin discoloration
- One 49 year old male experienced infection
- One 50 year old male experienced generalized application site reaction, pain, skin discoloration and exfoliated dermatitis
- One 79 year old female experienced generalized application site reaction, and skin ulcer

Reported outcomes included either treatment with a prescription drug, recovery or none (absence of data). A complete list of all reported adverse events for salicylic acid products included in the Spontaneous Reporting System is included in Appendix D.

FDA Adverse Event Reporting System (AERS) (1997–2001)

According to FDA's Adverse Event Reporting System, there were 41 reports of adverse events for products containing salicylic acid sold in the U.S. during the period from November 1, 1997 to the present. The reporter of eight of these reports classified salicylic acid as the primary suspect drug associated with the adverse reaction(s) following topical application of the product. These included six OTC drug products.

Clinique Anti-Itch Lotion & Cream containing E Acetate
Reaction: Unevaluable reaction
Male (age unreported)
Report Source: Unreported

Revco Wart Liquid
Reaction: Burns not otherwise specified (nos) Skin Infection nos
Gender/Age unreported
Report source: Consumer

Dr. Scholl's Soft Corn Removers Disc
Reaction: Dyspnoea not otherwise specified (nos), Hypersensitivity nos, Pruritus, Urticaria nos,
Male / 37 years old
Report Source: Foreign

Duofilm Liquid Topical Solution
Reaction: Abnormal endoscopy of small intestine, Haemoptysis, Mucous membrane disorder nos, Oral pain, Erythematous rash, Vomiting nos
Female / 13 years old
Report Source: Health professional

Duofilm
Reaction: Application site pain, Application site reaction nos, Drug maladministration, Erythematous rash, Skin injury, not otherwise specified (nos)
Male / 3 years old
Report Source: Unreported

Dr. Scholl's Clear Away Wart Remover Disc
Reaction: Application site erythema, Application site reaction nos, Blister, Cellulitus, Ecchymosis, Pyrexia, Swelling not otherwise specified (nos)
Male / 49 years old
Report Source: Consumer

A complete list of all reported adverse events for salicylic acid products included in the Adverse Events Reporting System is included in Appendix D.

Procter & Gamble Post Market Reported Adverse Events (1997 –2000)

The Procter & Gamble Beauty Care Safety Surveillance System is a post market electronic monitoring system that tracks and records adverse events for Procter & Gamble products sold in the U.S. and Canada. The majority of reported adverse effects that occurred between January, 1997 and December, 2000 included transient, acute dermatological effects that are occasionally associated with products that are used to treat or cleanse the skin. Cases of accidental ingestion, eye irritation, and irritant effects from inhalation were also reported along with cases of minor injuries (cuts and scratches) from unknown sources. The reported adverse effects that were skin related represented symptoms of acute dermatitis or primary irritation that included redness, inflammation, flushing, stinging, burning, dryness, peeling, flaking, cracking, itching, swelling, rash, bumps discoloration, and in extreme cases bleeding. Reported adverse effects associated with non-rinse off anti-acne products also included symptoms of acne. Individuals who experienced these reported adverse effects included males and females ranging in age from 1 to 83 years of age. A summary for all products is as follows:

Clearasil Clearstick

During this four year period, there was a total of 289 adverse events reported by consumers who used Clearasil Clearstick, a medicated leave-on anti-acne OTC drug product containing 2.0% salicylic acid. Eight of the 289 individuals requested, or were recommended for follow up by a physician for their condition. With only a few exceptions (a cut from an injury, cramping and headache) most of the reported adverse events were skin related including two cases each of reported welts, hives, and blisters, and twenty-five cases of reported acne. There were five recorded incidents of eye irritation from either direct or indirect contact with product.

Clearasil Pads

During this four year period, there was a total of 223 adverse events reported by consumers who used Clearasil pads, a medicated leave-on anti-acne OTC drug product containing 0.5% salicylic acid (Regular Strength) and 2% salicylic acid (Extra Strength). None of the individuals reporting these incidents requested, or were recommended for follow up by a physician. With the exception of one reported case each of headache and a runny nose, three cases of a scratch from an unknown injury, and four cases of eye irritation from direct or indirect contact with product, the remaining symptoms were dermatological in nature, identical to the those described above. There were 20 reported cases of acne.

Olay Daily Renewal Age Defying Facial Moisturizer

During this four year period, there was a total of 1306 adverse events reported by consumers who used Olay Daily Renewal Age Defying Cream, a leave-on cosmetic facial moisturizer containing 1.5% salicylic acid. Sixty-five of these individuals requested, or were recommended for follow up by a physician for their condition. There were 104 reported cases of eye effects from either direct or indirect contact with product, 45 reported cases of inhalation effects, two cases of accidental ingestion, and two cases of a cut or scratch (unknown source of injury). The remaining majority of all reported adverse effects were dermatological including 20 reported occurrences of hives and eight reported cases of welts associated with skin contact. No reported incident was considered serious. Consistent with newly introduced products, the frequency and number of related reported incidents for this product was highest within the first two years of marketing. As shown in Appendix D the number of reports dropped considerably for the subsequent two years of marketing, although the volume of units that were sold remained constant for each year. In the calendar year 2000, only 160 incidents were reported. This pattern is consistent with the reporting ratio of a **non-salicylic** acid moisturizer, Olay Daily Renewal Lotion, introduced with the cream. For comparison, from 1997 to 2000, approximately one reported incident occurred for every 3918 units of Olay Daily Renewal cream sold, and for the same time period, approximately one reported incident occurred for every 3059 units of Olay Daily Renewal lotion sold.

Olay Daily Renewal Age Defying Facial Cleanser

During this four year period, there was a total of 1249 adverse events reported by consumers who used Olay Daily Renewal Age Defying Cleanser, a cosmetic rinse off facial cleanser containing 2.0% salicylic acid. Thirty-one of these individuals requested, or were recommended for follow up by a physician for their condition. There were 74 reported cases of eye irritation from direct or indirect contact with product, 18 reported cases of acute effects from inhalation, six cases of accidental ingestion, and three cases of a cut or scratch, with the remaining majority of reported incidents being skin related. None of the reported incidents were considered serious. Consistent with newly introduced products, the frequency and number of related reported incidents for this product was highest within the first two years of marketing. As shown in Appendix D the number of reports dropped considerably for the subsequent two years of marketing, although the volume of units that were sold remained constant for each year. In the calendar year 2000, only 204 incidents were reported. From 1997 to 2000, approximately one reported incident occurred for every 6580 units sold.

Noxema leave-on products

During this four year period, there was a total of 952 adverse events reported by consumers who used Noxema Pads Regular Strength, Noxema Pads Extra Strength, Noxema Renewal Cream, or Noxema Astringent, all leave-on products containing 0.5%, 2.0%, 1.5% and 2.0% salicylic acid respectively. Seventeen of these individuals requested, or were recommended for follow up by a physician for their condition. The majority of all reported incidents were skin related and typical of the symptoms described above. These were followed by 58 reported cases of accidental ingestion, 22 reported cases of eye irritation from either direct or indirect contact with product, 29 reported cases of an unknown source of injury (cut, scratch), and 18 reported cases of adverse effects from inhalation.

A complete list of all reported adverse events for Procter & Gamble topical products containing salicylic acid in included in Appendix D.

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(1) "Brief Description with Caveats of System", Spontaneous Reporting System/Division of Epidemiology and Surveillance; Federal Drug Administration; January 30, 1996

(2) "Brief Description with Caveats of System", Adverse Event Reporting System/Office of Postmarketing Drug Risk Assessment; Federal Drug Administration; June 25, 1998

Attachment VII

Test Product Formulations

	#1	#2	#3	#4
Master Formula	**SWH160-152**	**SWH160-155**	**SWH094-136** **SWH160-159***	**SWH094-137** **SWH160-160***
Batch numbers	**SWH160-154** **SWH180-013**	**SWH160-156** **SWH180-012**	**SWH160-161*** **SWH180-014**	**SWH160-162*** **SWH180-015**
Ingredient				
Salicylic acid	0.0	2.0	1.0	0.0
Water	87.7	85.7	92.85	92.86
Cocamine oxide	[redacted]	[redacted]		
Cocamidopropyl betaine				
Sodium benzoate	0.2	0.2	0.2	
Disodium EDTA	0.1	0.1		
Phosporic acid	(0-1.0)	(0-8.0)		
Sodium hydroxide	(0-4.0)	(0-6.0)	(0-2.0)	
Sodium PCA			[redacted]	
Ammonium lauryl sulfate				
Simethicone				
Octyldecanol			0.2	0.2
Tetrasodium EDTA			0.1	0.1
Sulfuric acid			(0-2.0)	(0-2.0)
pH	7	3	3	7

*Master Formula SWH160-159 / Batch SWH160-161 was not analyzed.
Master Formula SWH160-161 / Batch SWH160-162 was not analyzed.

FILE MEMORANDUM

To: File **Date:** 5/30/01

From: Fred J. Hayes **R/L:** 10 years

Subject: Validation of Analytical Method for Salicylic Acid in Leave-on and Rinse-off Handwash Products

This correspondence summarizes results from the validation of an analytical (HPLC) method for determining the level of salicylic acid in limited-use handwash products. This validation was done in support of studies CRB 01-05-066-HB, CRB 01-05-065-HB, and CRB 01-04-063-HB. Since these products were of limited use and the matrices contain no interfering components, an abbreviated validation study was performed per Procter & Gamble Worldwide Quality Assurance SOP 012.0 (Effective date – August 11, 1997).

Analytical Methodology

A Beauty Care Analytical Test Method (GCAS No. 60073906) for Salicylic Acid entitled "ASSAY: Salicylic Acid in Products by HPLC" was used for this abbreviated validation. Briefly, this is a reversed-phase HPLC method with internal standard quantitation and is applicable to cleansers, creams, lotions, gels or solutions that contain salicylic acid. The method uses salicylamide as the internal standard with ultraviolet (UV) detection at 308 nm.

Validation Protocol

Per P&G Worldwide QA SOP 012.0, an abbreviated validation study was performed (spiked recovery at target level and method repeatability). Technical justification for this abbreviated protocol is based on the following: (a) these products were of limited use and (b) the matrices for the products contained no interfering components. Briefly, placebo product was spiked at 1% salicylic acid and 2% salicylic acid for the non-rinse off handwash (wipes) (Formula SWH94-137) and the rinse off handwash (Formula SWH160-152), respectively. For the spikes of SWH94-137 (1% product), 4 replicate spikes were prepared and analyzed. For the spikes of SWH160-152 (2% product), 5 replicate spikes were prepared and analyzed.

Validation Results

Results for the salicylic acid validation study described above are summarized in the tables below. These results meet the success criteria as outlined in P&G Worldwide QA SOP 012.0 for validation of methods.

Results for 1% Salicylic Acid Non-Rinse off Handwash (Placebo Formula SWH94-137)

Spike #	Theoretical level (%)	Measured (%)	Percent Recovery
1	1.11	1.12	100.9
2	1.03	1.04	101.0
3	1.06	1.08	101.9
4	1.06	1.07	100.9
Mean			**101.2**
% RSD			**0.48**

Results for 2% Salicylic Acid Rinse off Handwash (Placebo Formula SWH160-152)

Spike #	Theoretical level (%)	Measured (%)	Percent Recovery
1	2.09	2.10	100.5
2	1.98	1.99	100.5
3	2.06	2.07	100.5
4	1.99	2.00	100.5
5	1.98	2.00	101.0
Mean			**100.6**
% RSD			**0.22**

Raw data for this work is stored in Hardbound Notebook SP1022-127 to 130 and Looseleaf Notebook SWL1040-296 to 317.

Fred J. Hayes

Fred J. Hayes, Ph.D.
Beauty Care Analytical

TO: Swan/KC

SWTC BOX: Box 222

The Procter & Gamble Company
Personal Cleansing Skin Beauty Care Analytical Report
Sharon Woods Technical Center

Submission No. : 112622
Sample Description : 1% Sal Acid/[redacted]% PCA/[redacted]% ALS
Submission Date : 05/15/2001 01:17:55 PM
More Description : *none*
Study / Purpose: Class3 Study Rel
Submitter Ref : SWH180-014

Master Formula #: SWH94-136
Study Release / Method Validation Only

Completion Notes (If Any): fjh

Test Code	Method Ref.	Method Descriptor	112622 0000 Status: 3
9199	HPLC	Special Normal Phase HPLC	0 or 2 = Pending Review, 1 or 3 = Reviewed

9199	Result	Notebook No.	Date Completed
Phase HPLC	Entered	SWL1040-296	5/21/01
9199	Comment		
Phase HPLC	Not Entered		

(Result.Phase HPLC)
0.94 % SALICYLIC ACID

Test Code	Method Ref.	Method Descriptor	112622 0001 Status: 3
2134	pH - FPPH100A	pH Value without Dilution	0 or 2 = Pending Review, 1 or 3 = Reviewed

2134	Result	Notebook No.	Date Completed
pH Value	2.98	SWL873-034	5/21/01
2134	Comments		
pH Value	Not Entered		

Fred J. Hayes 5-22-01
Analytical Reviewer Date

Note: Without Analytical Signature, further review of the data may still be necessary to ensure the accuracy of the results

TO: Swan/KC

SWTC BOX: Box 222

The Procter & Gamble Company
Personal Cleansing Skin Beauty Care Analytical Report
Sharon Woods Technical Center

Submission No. : 112623
Sample Description : 0% Sal Acid/[redacted]% PCA/[redacted]% ALS
Submission Date : 05/15/2001 01:19:29 PM
More Description : *none*
Study / Purpose: Class3 Study Rel
Submitter Ref : SWH180-015

Master Formula #: SWH94-137
Study Release / Method Validation Only

Completion Notes (If Any): fjh

Test Code	Method Ref.	Method Descriptor
9199	HPLC	Special Normal Phase HPLC

112623 0000 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

9199	Result	Notebook No.	Date Completed
Phase HPLC	Entered	SWL1040-296	5/21/01
9199	Comment		
Phase HPLC	Not Entered		

(Result.Phase HPLC)
0 % SALICYLIC ACID

Test Code	Method Ref.	Method Descriptor
2134	pH - FPPH100A	pH Value without Dilution

112623 0001 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

2134	Result	Notebook No.	Date Completed
pH Value	6.91	SWL873-034	5/21/01
2134	Comments		
pH Value	Not Entered		

Fred J. Hayes 5-22-01
Analytical Reviewer Date

Note: Without Analytical Signature, further review of the data may still be necessary to ensure the accuracy of the results

ISA

TO: Swan/KC

SWTC BOX: Box 222

The Procter & Gamble Company
Personal Cleansing Skin Beauty Care Analytical Report
Sharon Woods Technical Center

Submission No. : 112619
Sample Description : 2% Sal Acid Hand Wash
Submission Date : 05/15/2001 01:13:27 PM
More Description : *none*
Study / Purpose: Class3 Study Rel
Submitter Ref : SWH180-012

Master Formula #: SWH160-155
Study Release / Method Validation Only

Completion Notes (If Any): fjh

Test Code	Method Ref.	Method Descriptor
9199	HPLC	Special Normal Phase HPLC

112619 0000 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

9199	Result	Notebook No.	Date Completed
Phase HPLC	Entered	SWL1040-296,309	5/21/01
9199	Comment		
Phase HPLC	Not Entered		

(Result.Phase HPLC)

SAMPLE #,RESULT

SWH160-157A,2.24% SALICYLIC ACID
SWH160-157B,2.21% SALICYLIC ACID
SWH160-157C,2.23% SALICYLIC ACID
SWH160-157D,2.23% SALICYLIC ACID
SWH160-157E,2.24% SALICYLIC ACID

Test Code	Method Ref.	Method Descriptor
2134	pH - FPPH100A	pH Value without Dilution

112619 0001 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

2134	Result	Notebook No.	Date Completed
pH Value	3.01	SWL873-034	5/21/01
2134	Comments		
pH Value	Not Entered		

Fred J. Hayes — Analytical Reviewer

5-22-01 — Date

Note: Without Analytical Signature, further review of the data may still be necessary to ensure the accuracy of the results

12 A

TO: Swan/KC

SWTC BOX: Box 222

The Procter & Gamble Company
Personal Cleansing Skin Beauty Care Analytical Report
Sharon Woods Technical Center

Submission No. : 112621
Sample Description : 0% Sal Acid Hand Wash
Submission Date : 05/15/2001 01:15:47 PM
More Description : *none*
Study / Purpose: Class3 Study Rel
Submitter Ref : SWH180-013

Master Formula #: SWH160-152
Study Release / Method Validation Only

Completion Notes (If Any): fjh

Test Code	Method Ref.	Method Descriptor
9199	HPLC	Special Normal Phase HPLC

112621 0000 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

9199	Result	Notebook No.	Date Completed
Phase HPLC	Entered	SWL1040-296	5/21/01
9199	Comment		
Phase HPLC	Not Entered		

(Result,Phase HPLC)
0% SALICYLIC ACID

Test Code	Method Ref.	Method Descriptor
2134	pH - FPPH100A	pH Value without Dilution

112621 0001 Status: 3
0 or 2 = Pending Review, 1 or 3 = Reviewed

2134	Result	Notebook No.	Date Completed
pH Value	6.96	SWL873-034	5/21/01
2134	Comments		
pH Value	Not Entered		

Fred J. Hayes 5-22-01
Analytical Reviewer Date

Note: Witnout Analytical Signature, further review of the data may still be necessary to ensure the accuracy of the results

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BEAUTY CARE MASTER FORMULA

IN-PROCESS OR FNISHED PRODUCT

COSMETIC [ ]
OTC DRUG [X]
IND/NDA DRUG [ ]

P&G [ ]
COMPETITOR [ ]

PRODUCT NAME: Sal. Acid Formula - 1% Sal. Acid

MASTER FORMULA #: SWH160.159

COUNTRY OF MANUFACTURE: United States

RMS, GCAS or Notebook #	*	TRADE OR COMMON NAME	CTFA NAME	CAS #	PERCENT COMPOSITION	
					As Added	Chem. Content
10000850	*	Salicylic Acid	Salicylic Acid	69-72-7	1.00	1.00
BX2640		PCA	PCA	98-79-3	[redacted]	[redacted]
10000850		Ammonium Laurel Sulfate	Ammonium Laurel Sulfate	32612-48-9	[redacted]	[redacted]
48082		Sodium Hydroxide**	Sodium Hydroxide **	1310-73-2	0.00	0.00
BX2450		Phosphoric Acid **	Phosphoric Acid **	7664-38-2	0.00	0.00
10045437		Dissolvine NA - 2X	Disodium EDTA	139-33-3	0.11	0.10
48062		Sodium Benzoate	Sodium Benzoate	532-32-1	0.20	0.20
BX236		Water	Water	7732-18-5	91.29	93.10
				TOTAL	100.00	100.00 ~~0.00~~

JEC 5/7/01

*Active Ingredient

** Use to pH to 2.9 -- phosphoric acid range from 0 - 8.5 as added; 0 - 8 chemical content
sodium hydroxide range from 0 - 8 as added; 0 - 6 chemical content

Compiled by (print): Heather Cornell
Verified by (print)**: KYLE C SWAN
**cosm-optional
Comments:

Signature/Date: Heather Cornell 5/7/01
Signature/Date: Kyle C 5/7/01

PAGE 000159-000160 SWH NOTEBOOK ☐ ATTACHMENTS

SIGNATURE _____ DATE _____

WITNESSED BY _____ DATE _____

Origin 062599

Procter&Gamble Restricted Data

U.S. PATENT NOs. 5,754,933 5,171,040

BEAUTY CARE MASTER FORMULA

IN-PROCESS OR FNISHED PRODUCT

COSMETIC [ ]
OTC DRUG [X]
IND/NDA DRUG [ ]

P&G [ ]
COMPETITOR [ ]

PRODUCT NAME: Sal. Acid Formula - 1% Sal. Acid, pH = 7

MASTER FORMULA #: SWH160.160

COUNTRY OF MANUFACTURE: United States

RMS, GCAS or Notebook #	*	TRADE OR COMMON NAME	CTFA NAME	CAS #	PERCENT COMPOSITION	
					As Added	Chem. Content
BX2640		PCA	PCA	98-79-3	[redacted]	[redacted]
10000850		Ammonium Laurel Sulfate	Ammonium Laurel Sulfate	3212-48-9	[redacted]	[redacted]
48082		Sodium Hydroxide**	Sodium Hydroxide **	1310-73-2	0.00	0.00
BX2450		Phosphoric Acid **	Phosphoric Acid **	7664-38-2	0.00	0.00
10045437		Dissolvine NA - 2X	Disodium EDTA	139-33-3	0.11	0.10
48062		Sodium Benzoate	Sodium Benzoate	532-32-1	0.20	0.20
BX236		Water	Water	7732-18-5	92.29	94.10
				TOTAL	100.00	100.00

*Active Ingredient

** Use to pH to 7.0 – phosphoric acid range from 0 - 8.5 as added; 0 - 8 chemical content
sodium hydroxide range from 0 - 8 as added; 0 - 6 chemical content

Compiled by (print): Heather Cornell
Verified by (print):** KYLE C SWAN
**cosm-optional
Comments:

Signature/Date: Heather Cornell 5/4/01
Signature/Date: Kyle C 5/7/01

PAGE 000160-000160 SWH NOTEBOOK ☐ ATTACHMENTS

SIGNATURE _____ DATE _____

WITNESSED BY _____ DATE _____

Origin 062599

Procter&Gamble Restricted Data

U.S. PATENT NOs. 5,754,933 5,171,040

PRODUCT NAME: 20% Ethanol + No Sal Acid pH=3
STUDY #:
TEST CODE:
LOCATION: PRL Lab B1E

MASTER FORMULA #: SWH94-127
BATCH #: SWH94-127
BATCH SIZE: 1000 g
Class 3 ____ Class 2 X

Operator and witness:

Karl Wei
Name(Printed)
Meredith Ireland (MOL)
Name(Printed)

Kent S. Wei KSW 3-28-01
Signature Initial/Date
Meredith O. I. MOL 3-28-01
Signature Initial/Date

Step	MAKING INSTRUCTIONS/TIME	RMS#	LOT #	OBS	% ACTIVE	CHEMICAL % W/W	AS ADDED % W/W	TARGET WT. (g)	ACTUAL WT. (g)	DONE/ ADDED BY	CHECKED BY (class 3 only)
1	Purge operating area of all materials and equipment not associated with this batch.										
2	Start time: 8:30 am									MOL	
3	Weigh out all materials on Mettler PM2000 balance.									MOL	
4	Add the following ingredients to the main mix									MOL	
5	Water Distilled	BX236	56		100.00	80.00	80.00	800.00	801.30 g	MOL	
6	Ethanol	45105	239		100.00	20.00	20.00	200.00	204.73 g	MOL	
7	Keep agitation and solution becomes clear. Then add:									MOL	
8	Mix well									MOL	
9	Adjust pH to 3 +/- 0.05 using calibrated pH meter.									MOL	
10	Starting pH= 2.9									MOL	
11	Sodium Hydroxide	48082			30.00					MOL	
12	Hydrochloric Acid				30.00					MOL	
13	Final pH= 3.0									MOL	
14	QS with distilled water to 100%									MOL	
15	Water Distilled	BX236				QS				MOL	
16	Pour lotion into container and record weight.									MOL	
17	End time: 9:01 am									MOL	
			Totals			#REF!	100.000	1000.00	1005.1	MOL	

Maximum Yield (%) expected = 95%
Minimum Yield (%) expected = 105%
ACTUAL YIELD WT. 1005.1

Yield (%) = AL WEIGHT / TARGET WEIGHT = 1045.1 / 1000 x 100 = 100.5%

Performed By/Date: MOL 3-28-01
Checked By/Date: Kent S. Wei 3-28-01

SIGNATURE ______ DATE ______
WITNESSED BY ______ DATE ______
PAGE 00127-00094 SWH NOTEBOOK ☐ ATTACHMENTS ______

Procter & Gamble Restricted Data
Orig'a 06259
U.S. PATENT NOS. 5,154,933 5,171,040

PRODUCT NAME: 20% Ethanol + No Sal Acid pH=7
STUDY #:
TEST CODE:
LOCATION: PRL Lab B1E

MASTER FORMULA #: SWH94-128
BATCH #: SWH94-128
BATCH SIZE: 1000 g
Class 3 ____ Class 2 X

Operator and witness:

Karl Wei — Karl S. Wei — KSW 3/29/01
Name(Printed) — Signature — Initial/Date

Meredith Leland (MOL) — Meredith O. Leland — MOL 3-28-01
Name(Printed) — Signature — Initial/Date

Step	MAKING INSTRUCTIONS/TIME	RMS#	LOT #	OBS	% ACTIVE	CHEMICAL % W/W	AS ADDED % W/W	TARGET WT. (g)	ACTUAL WT. (g)	DONE/ ADDED BY	CHECKED BY (class 3 only)
1	Purge operating area of all materials and equipment not associated with this batch.									MOL	
2	Start time: 3:20 pm									MOL	
3	Weigh out all materials on Mettler PM2000 balance.									MOL	
4	Add the following ingredients to the main mix.									MOL	
5	Water Distilled	BX236	58		100.00	80.00	80.00	800.00	801.9g	MOL	
6	Ethanol	45INC	279		100.00	20.00	20.00	200.00	199.4g	MOL	
7	Keep agitation until solution becomes clear. Then add.									MOL	
8	Mix well 3:27:05									MOL	
9	Adjust pH to 3.47-3.05 using calibrated pH meter.									MOL	
10	Starting pH= 2.5									MOL	
11	Sodium Hydroxide	48082			30.00					MOL	
12	Hydrochloric Acid				30.00					MOL	
13	Final pH= 3.5									MOL	
14	QS with distilled water to 100%									MOL	
15	Water Distilled	BX236				QS				MOL	
16	Pour lotion into container and record weight.									MOL	
17	End time: 3:30 pm									MOL	
			Totals			WNEI	100.000	1000.00	1001.3	MOL	

Maximum Yield (%) expected = 105%
Minimum Yield (%) expected = 102%
ACTUAL YIELD WT.: 1001.3

Yield (%) = ACTUAL WEIGHT / TARGET WEIGHT = 1001.3 / 1000 x 100 = 100%

Performed By/Date: MOL 3-28-01
Checked By/Date: 3-28-01

SIGNATURE _____ DATE _____

WITNESSED BY _____ DATE _____

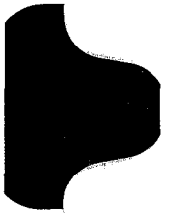
ATTACHMENTS _____

PAGE 00128-00094 SWH NOTEBOOK

Procter&Gamble Restricted Data

Origin 062599

U.S. PATENT NOs. 5,764,933
5,771,040



Attachment VIII

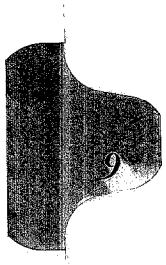
Antimicrobial Spectrum – Minimal Inhibitory Concentration (ug/mL)

Test Organisms (10^6 CFU/mL)	Minimal inhibitory concentration (ug/mL) pH 3.2 (serial dilution test; incubation times 24 and 72 hrs)
Staphylococcus aureus	1250
Escherichia coli	1250
Klebsiella pneumoniae	1250
Pseudomonas aeruginosa	2500
Pseudomonas fluorescens	1250
Pseudomonas cepacia	2500
Candida albicans	2500
Aspergillus niger	2500
Penicillium notatum	2500

Cosmetic and Drug Preservation Principles and Practices; Kabara, Jon J., editor; Marcel Dekker, Inc.; New York and Basel; p 673

Test Organisms (10^8 /mL yeasts & dermatophytes) (10^9/mL bacteria)	Minimal inhibitory concentration (ug/mL) (incubation times of 24 hrs bacteria, 48 hrs yeast & 96 hrs dermatophytes)
Aspergillus elegans	2000
Staphyloccus aureus	2000
Streptococcus pyog.	3000
Escherichia coli	3000
Proteus vulgaris	2000
Pseudomonas aerugin	3000
Trichophyton mentagrophyts	750
Trichophyton Quinckeanum	450
Trichophyton tonsurans	550
Trichophyton Schonleinii	600
Trichophyton verrucosum	600
Epidermophyton floccosum	700
Keratinomyces ajelloi	70
Torulopsis famata	2000
Rhodotorula mucilaginosa	2000
Candida parapsilosis	2000
Trichophyton rubrum	550
Mikrosporum gypseum	650
Candida albicans	2000
Candida tropicalis	2000

Scherrer, M.; Knusel F; et. al.; "Antimicrobial activity of broad spectrum antimicrobial agents, with special reference to salicylic acid"; Mykosen; Vol 7 (6); July 1, 1971; pp 323-234



Attachment IX

Time Kill Results

Simple Solutions

Log Reduction from Control							
Formulation	**Notebook Number**	**Time Point**	***P. aeruginosa* 9027**	***S. choleraesius* 10708**	***S. epidermis* 12228**	***E. coli* 11229**	***S. aureus* 27217**
1% Sal. Acid 20% Ethanol @ pH=3	SWH94-126	30 sec	≥5.0	≥4.2	≥4.4	≥3.2	≥3.2
		1 min	≥5.0	≥4.2	≥4.4	≥3.2	≥3.2
		5 min	≥5.0	≥4.2	≥4.4	≥3.2	≥3.2
20% Ethanol @ pH=7	SWH94-128	30 sec	0.0	0.0	0.1	0.1	0.0
		1 min	0.2	0.0	0.2	0.0	0.0
		5 min	0.8	0.3	1.2	0.0	0.9
20% Ethanol @ pH=3	SWH94-127	30 sec	0.4	0.1	0.1	0.0	0.1
		1 min	0.5	0.2	0.5	0.1	0.3
		5 min	1.6	3.3	4.4	0.8	2.4

*All solutions were tested at full concentration.

Test Product 3 Non rinse-off formulation containing 1% salicylic acid

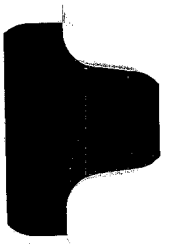
Log Reduction from Control							
Formulation	**Notebook Number**	**Time Point**	***P. aeruginosa* 9027**	***S.epidermis* 12228**	***S.choleraesius* 10708**	***E. coli* 11229**	***S. aureus* 27217**
1% SA [redacted]PCA [redacted]ALS pH=3.0	SWH160-161	30 sec	≥4.6	≥4.4	≥5.1	4.7	≥4.7
		1 min	≥4.6	≥4.4	≥5.1	4.4	≥4.7
		5 min	≥4.6	≥4.4	≥5.1	≥4.9	4.4
Placebo: [redacted]PCA [redacted]ALS pH= 7.0	SWH160-162	30 sec	0.2	≥4.4	0.1	0.5	4.3
		1 min	0.3	≥4.4	0.0	0.4	4.3
		5 min	0.5	≥4.4	0.1	0.9	4.3

*All solutions were tested at full concentration.

Test Product 2 Rinse-off formulation containing 2% salicylic acid

Log Reduction from Control							
Formulation	**Notebook Number**	**Time Point**	***P. aeruginosa* 9027**	***S.epidermis* 12228**	***S.*choleraesius *10708***	***E. coli* 11229**	***S. aureus* 27217**
2% SA [redacted]cocamidopropyl betaine [redacted]amine Oxide pH= 3.0	SWH160-156	30 sec	≥4.7	≥4.5	≥4.7	≥4.8	1.0
		1 min	≥4.7	≥4.5	≥4.7	≥4.8	1.9
		5 min	≥4.7	≥4.5	≥4.7	≥4.8	≥4.5
Placebo: [redacted]cocamidopropyl betaine [redacted]amine oxide pH= 7.0	SWH160-154	30 sec	0.4	2.9	2.3	1.7	0.2
		1 min	0.6	3.3	3.4	1.9	0.2
		5 min	1.0	4.2	≥4.7	2.0	0.6

*All solutions were tested at 0.2% concentration.



Attachment X

Pharmacology of Salicylic Acid

MARTINDALE - The Complete Drug Reference

Salicylic Acid

- **PHYSICAL AND PHARMACEUTICAL PROPERTIES**
  - Synonyms: Acido Ortoxibenzoico; Acidum Salicylicum; Salizylsaure.
  - Chemical Name: 2-Hydroxybenzoic acid.
  - Molecular Formula: C(7)H(6)O(3)
  - Molecular Weight: 138.1
  - CAS Registry: 69-72-7.
  - Pharmacopoeias: In Chin., Eur. (see Ref.), Int., Jpn, Pol., and US.
  - 2701/a4-c
  - Pharmacopoeial description.
  - Ph. Eur.: White or colourless acicular crystals or a white crystalline powder. Slightly soluble in water; freely soluble in alcohol and in ether; sparingly soluble in dichloromethane. Protect from light.
  - USP 24: White crystals, usually in fine needles or a white, fluffy, crystalline powder. The synthetic form is white and odourless but if prepared from natural methyl salicylate it may have a slightly yellow or pink tint, and a faint, mint-like odour. Soluble 1 in 460 of water, 1 in 15 of boiling water, 1 in 3 of alcohol, 1 in 45 of chloroform, 1 in 3 of ether, and 1 in 135 of benzene.
- **ADVERSE EFFECTS AND PRECAUTIONS**
  - Salicylic acid is a mild irritant and application of salicylic acid preparations to the skin may cause dermatitis. Salicylic acid is readily absorbed through the skin and symptoms of acute systemic salicylate poisoning (see Aspirin, Ref.) have been reported after excessive application of salicylic acid to large areas of the body; several deaths have occurred, mainly in children. To minimise absorption following topical application salicylic acid should not be used for prolonged periods, in high concentrations, on large areas of the body, or on inflamed or broken skin. Contact with mouth, eyes, and other mucous membranes should be avoided. It should also be used with care on the extremities of patients with impaired peripheral circulation or diabetes.
  - There has been a report that application of 2% salicylic acid in a cream base before phototherapy delayed or reduced the clearance of psoriatic lesions when compared with the use of the base alone. (1) It was suggested that salicylic acid might have been acting as a photoprotective agent (1) but a later study (2) failed to confirm this. However, emulsifying ointment was found to have such an effect and it was recommended that it should not be used before phototherapy or in phototesting procedures. (2)
  - 1. Kristensen B, Kristensen O. Salicylic acid and ultraviolet B for psoriasis. Lancet 1989; ii: 1109-10.
  - 2. Cox NH, Sharpe G. Emollients, salicylic acid, and ultraviolet erythema. Lancet 1990; 335: 53-4.

- **USES AND ADMINISTRATION**

    - Salicylic acid has keratolytic properties and is applied topically in the treatment of hyperkeratotic and scaling skin conditions such as dandruff and seborrhoeic dermatitis (Ref.), ichthyosis (Ref.), psoriasis (Ref.), and acne (Ref.). Initially a concentration of about 2% is used, increased to about 6% if necessary, though a wider range of concentrations has been used. It is often used in conjunction with other drugs, notably coal tar.

    - Preparations containing up to 60% salicylic acid have been used as a caustic for the removal of plantar warts (Ref.), corns, or calluses.

    - Salicylic acid also possesses fungicidal properties and is used topically in the treatment of dermatophyte skin infections (see Ref.).

- **PROPRIETARY NAMES**

    - A Curitybina, Acnex, Acnisal, Aknefug-liquid, Anti-Acne Control Formula, Anti-Acne Spot Treatment, Biactol Antibacterial Double Action Pads (FM), Blemish Control, Callicida Globodermis, Callicida Gras, Callicida Salve, Callofin, Callus Salve (FM), Carnation, Ciella, Clabin, Clean & Clear Deep Cleaning Astringent, Clean & Clear Invsible Blemish, Clear Away, Clear Away (FM), Clear Pore, Clear Pore Treatment (FM), Clearail Pads, Clearasil Cleanser, Clearasil Clearstick, Clearasil Dual Action Pads, Clearasil Gel soin de nuit (FM), Clearasil Medicated Astringent (FM), Clearasil Medicated Wipes, Clearasil Nightclear, Clearasil Pads, Clearex, Clearskin 2 Medicated Wash, Clearskin 2 Triple Action, Clearskin Cleansing, Clearskin Medicated Wash, Clearskin Overnight Acne Treatment, Compound V, Compound W, Compound W Plus, Coricide le Diable, Coricides feuille de saule (FM), Corn Solvent (FM), Cornina Hornhaut (FM), Cornina Huhneraugen (FM), Curakalos, DHS Sal (FM), Dermi-cyl Schrunden, Disques Coricides, Dr Scholl's Callus Removers, Dr Scholl's Clear Away, Dr Scholl's Corn Removers, Dr Scholl's Corn/Callus Remover, Dr Scholl's Wart Remover, Duofilm, Duoforte, Duoplant, Efasit N (FM), Egocappol (FM), Egozite Cradle Cap, Feuille de Saule, Formule W, Fostex Acne Medication Cleansing, Fostex Medicated Cleansing, Freezone, Freezone (FM), Gehwol Schalpaste, Gordofilm, Guttaplast, Gyan (FM), Hansaplast Hornhaut-Pflaster, Hansaplast Huhneraugen-Pflaster, Humopin N (FM), Hydrisalic, Ionil, Ionil (FM), Ionil Plus, Ionil Scalp Cleanser, Ionil-T, Ionil-T Plus, Isophyl (FM), Jiffy Corn Plasters (FM), John Plunketts Sunspot Cream (FM), Johnsons Clean & Clear Skin Balancing Moisturiser, Keralyt, Keralyt (FM), Keranon, Kertyol, Listerex (FM), Lygal Kopfsalbe N, MG217 Sal-Acid, Mediplast, Mosco, Mudd Acne (FM), Neostrata AHA Astringent Acne, Neutrogena Anti-Acne, Neutrogena Healthy Scalp Anti-Dandruff, Nova Perfecting Lotion (FM), Noxacorn (FM), Noxema 2-in-1, Occlusal, Off-Ezy, Oil-Free Acne Wash (FM), Oxy Balance, Oxy Clean Pore, Oxy Control (FM), Oxy Deep Pore, Oxy Medicated Pads, Oxy Night Watch, Oxy Night Watch (FM), P & S, Panscol, Pansements Coricides, Paplex Ultra (FM), Pickles Foot Ointment, Pommade Mo Cochon, Propa PH, PropapH, Psor-a-set, Psorimed, Radikal-Salicylcollodicum (FM), Rheumagutt-Bad N (FM), S/Gel, SCR, Sal-Acid, Sal-Clens (FM), Sal-Plant, Salac, Salact (FM), Salactic Film, Salatac, Salicyl, Salicylic Acid Gel USP 24, Salicylic Acid Ointment BP 2000, Salicylic Acid Plaster USP 24, Salicylic Acid Topical Foam USP 24, Salikaren, Salseb, Salsyvase, Scholl 2-Drop Corn Remedy, Scholl Callous Removal, Scholl Callus Remover, Scholl Clear Away, Scholl Corn Removal, Scholl Corn Remover, Scholl Corn Salve (FM), Scholl Corn, Callus Plaster Preparation (FM), Scholl Corn/Callous Removers, Scholl One Step, Scholl Verucca Removal, Scholl Wart Remover, Scholl Zino, Schrundensalbe Dermi-cyl, Sebcur, Sebium K2, Sebucare, Septisol (FM), Sicombyl, Soluver, Soluver Plus, Sophtal-POS N, Squamasol, Stri-Dex Clear, Sulfoam, Sunspot, Ten-O-Six (FM), Trans-Plantar, Trans-Ver-Sal, Trans-Ver-Sal AdultPatch, Trans-Ver-Sal PediaPatch, Trans-Ver-Sal PlantarPatch, Transvercid, Unguento Morryth, Urgo-N Huhneraugenpflaster, Urgocall, Vericaps, Verruca Treatment, Verrucid, Verrucosal (FM), Verrugon, Verrupath, Verruplan, Verucca Removal System, Viranol (FM), Wart Remover, Wart Remover (FM), Wart-Off, Wartex, X-Seb

- **MULTI-INGREDIENT PREPARATIONS**

    - A Curitybina, ATS (FM), Acerbine, Acerbine (FM), Acerbiol, Acnaveen, Acne Creme, Acne Lotion, Acne-Ban (FM), Acne-Med (FM), Acnidazil (FM), Acno, Acnosan, Acnotex, Adasept, Adexone, Akne-Medice Kombipackung (FM), Aknecin, Aknederm N, Aknedertim (FM), Aknelan Lotio (FM), Aknichthol, Aknichthol Dexa (FM), Aknichthol N, Aknin, Albicort Compositum, Albicort Oticum, Alcusal, Alfa Acid, Alpha Cade, Alpha Keri Tar, Alpha Septol, Alpicort, Alpicort

F, Alpicort F neu, Alpicort N, Am-O-Lin, Anaxeryl, Animbo-N (FM), Animbo-Tinktur (FM), Anthraderm, Anti-Acne Formula for Men (FM), Antinea (FM), Antipeol, Antiphlogistine, Antiverrugas, Aporil, Apotheker Bauer's Huhneraugentinktur, Apsor (FM), Arthrex (FM), Aserbine, Aserbine (FM), Aveeno Acne Bar, Aveeno Cleansing Bar, Aveenobar (for acne) (FM), Balsamo Analgesico, Balsamo Analgesico Labesfal, Balsamo Analgesico Sanitas, Baume Esco, Baume Esco Forte, Baume Saint-Bernard (FM), Bazalin, Bazuka, Bensal HP, Benzoderm (FM), Benzoic and Salicylic Acids Ointment USP 24, Beprosalic, Beta-S, Betacortone S, Betaderm, Betadermic, Betamethason Plus, Betnesalic, Betosalic, Biolan Cad (FM), Biolan Tar (FM), Boralina, British Army Foot Powder, Bruciaporri, Buccothymol (FM), CT Pommade, Calicida Indiano, Callicida Brujo, Callicida Brum, Callicida Cor Pik, Callicida Cor Pik Stick (FM), Callicida Durcall, Callicida Rojo, Callivoro Marthand, Callix D, Calloverk (FM), Calope, Canthacur-PS, Cantharone Plus, Cantharone Plus (FM), Capasal, Carl Baders Divinal, Clabin, Clearasil Cream (FM), Clearasil Disques (FM), Clearasil Double Clear, Clearasil Double Textured Pads, Clearasil Gel de soin invisible (FM), Clearasil Medicated Cleanser (FM), Clearasil Medicated Foam (FM), Clearskin 2 Overnight Acne Treatment, Clearskin Acne Defense Stick, Clearstick (FM), Cliniderm, Co Bucal, Coal Tar and Salicylic Acid Ointment BP 2000, Coalgel (FM), Cocois, Cold Cream Salicyle, Collomack, Collomack (FM), Compound Benzoic Acid Ointment BP 2000, Consablitz (FM), Contrheuma Bad L, Corn Removing Liquid, Corn Salve (FM), Corneolent (FM), Cornkil, Corti Jaikal, Cortidexason-S (FM), Crema Grasa (FM), Crema Neutra (FM), Criniton, Crino-Kaban N, Crinohermal (FM), Crinohermal P (FM), Cuplex, Curacallos Pedykur (FM), Curumbil (FM), DDD, DDD (FM), Decongestine (FM), Depurativo Richelet, Derma Care, DermaVeen Acne (FM), Dermacide, Dermacide (FM), Dermaknin (FM), Dermatar, Dermatech Wart Treatment, Dermic, Dermicon, Dermijabon Antiseborreic (FM), Dermisdin, Dermofytol, Dermosed, Dermycose, Dexacrinin (FM), Dexasalyl, Dexasalyl (FM), Dibetop Q, Diprosalic, Dithranol Paste BP 2000, Dithrasal, Dithrolan (FM), Docut Num 1 (FM), Dolex, Dolopax (FM), Donalg, Drytex, Duofilm, Duoplant, Eau Precieuse, Eczema Ointment, Eczema Ointment (FM), Ederphyt, Edoltar, Efasit N (FM), Ego Prickly Heat Powder (FM), Egomycol, Egomycol (FM), Egozite Cradle Cap, Ell-Cranell, Emersal, Enelbin-Paste N, Enelbin-Salbe N, Euvaderm (FM), Euvaderm N (FM), Eviprostat, Examex (FM), Extracort Tinktur N, Fertomcidina-U, Fitex E (FM), Flumasalen, Flutenal Sali, Fortalis, Fostex Medicated, Fostex Medicated Cleansing Bar (FM), Fungi-Nail, Fungiderm N (FM), Fungol, Furodermil (FM), Gehwol Huhneraugen Tinktur, Gehwol Huhneraugenpflaster, Gehwol Nagelpilz, Gelcosal, Gelictar Fort, Gets-It, Glido (FM), Glido Neomycine (FM), Gynescal (FM), Hairscience, Halciderm, Halciderm (FM), Hebrin, Histajodol N, Hongosan, Humal, Ibaril med salicylsyra, Ibaril med salicylsyre, Ichtyosoft, Igitur-Rheumafluid (FM), Igitur-antirheumatische, Ingelan, Ingrown Toe Nail Salve (FM), Iodermol, Ionax Astringent, Ionax T, Ionax T (FM), Ionil, Ionil Plus, Ionil-T, Ionil-T (FM), Jadit, Jadit (FM), Jadit P (FM), Jadit-Hydrocortisone (FM), Jaikal, Johnsons Clean & Clear Daily Facial Moisturiser, Johnsons Clean & Clear Invisible Blemish Treatment, Johnsons Clean & Clear Oil Controlling Toner, Jonil T (FM), K(5) "spezial" (FM), Kalloplast, Kalostop, Karoyan S, Kenacort-A, Kenacort-T comp, Kenalcol, Kenalog, Kenalog med Salicylsyre, Kerafilm, Keralac Plus, Kerasal, Komed (FM), Kreuzlinger Klosterliniment, Kusmin (FM), Kytta-Nagelsalbe (FM), Laccoderme a l'huile de cade, Laccoderme acide salicylique (FM), Lactisol (FM), Ladivonsim Liquido (FM), Lapices Epiderm Metadier, Lapiz Termo Compositum (FM), Lauroderme, Lauromentol, Lini-Bombe (FM), Linimento Naion, Locacorten Tar, Locacorten Tar (FM), Locacorten med Salicylsyre, Locacortene Tar, Localone, Locasalen, Locasalen (FM), Locasalene (FM), Locorten Tar (FM), Lorinden T, Losalen, Lotio decapans, Lucil (FM), Lucretin, Lygal E Tinktur, Lygal Kopftinktur, MG217 Medicated Tar-Free, MG400, Malatex (FM), Malveol, Marciderm (FM), Mazon Medicated Cream, Mazon Medicated Shampoo, Medi-Dan, Meted, Micocid, Micofim, Micofoot, Micotiazol, Micotissim, Mobilat, Mobilat (FM), Mobilat N, Mobilisin, Mokoto (FM), Monphytol, Monphytol (FM), Moorbad-Saar N, Movelat, Movilat, Movilisin, Myco-Jellin (FM), Myco-Synalar, Mycoderm, Mycozol (FM), Nacient Sulf Con Ac Sali (FM), Neo Zeta-Foot (FM), Neo-Phlogicid, NeoCeuticals Clear Skin, Neoceuticals Clear Skin Solution, Neostrata AHA Blemish, Nerisalic, Neutrogena T/Sal, Night Cast R (FM), Night Cast Regular Formula (FM), Nitroina, Nitrol, Node Tar (FM), Noxacorn, Omcilon A, Onico Fitex, Onycho Phytex, Onycho Phytex (FM), Onymyken S (FM), Opplin, Optal, Oratol, Oticane (FM), Oturga, Oxidermiol Lassar, Oxipor, Oxipor (FM), Oxy Clean Medicated, Oxy Clean Medicated (FM), Oxy Clean Soap (FM), Oxy Cleanser, Oxy Dots, Oxy Duo Pads, P & S Plus, Pantocrinale, Paplex (FM), Paps, Pasta Cool, Pasta Lassar Orravan, Pasta boli, Pasta rubra salicylata, Pelarol (FM), Peneytol (FM), Pentrax, Pernox, Phytex, Phytex (FM), Phytocil (FM), Phytoderm Compositum, Pickles Corn Caps, Pilison, Pinal N, Pirrolfungin, Pitrisan, Pixor Stick Anti-acne N, Plesial (FM), Po Antisseptico, Polytar AF, Posalfilin, Pragmatar, Pragmatar (FM), Procor S, Provegol Shampooing Cadique Compose (FM), Psocortene (FM), Psodermil, Psor-Asist, Psoralon

MT, Psoralon MT (FM), Psorantral, Psoriasis-Salbe M (FM), Psorigerb N, Psorin, Psorin (FM), Psorinase, Psorispray (FM), Pyolysin, Pyralvex, Pyralvex (FM), Quocin, Radian-B, Radio Salil, Rado-Salil, Resaltar (FM), Rheumalan, Rheumaliment (FM), Rheumasan, Rheumasan N, Riosol F (FM), Rivescal Tar, Rublex D, S-Coaltar (FM), SLT, SM-33, SM-33 Adult Formula, Sal-Oil-T, Salactol, Salatac, Salatac Gel, Salder S, Salhumin, Salhumin (FM), Salhumin Rheuma-Bad, Salhumin Sitzbad N, Salhumin Teilbad N, Sali-Decoderm, Salicylic Acid Collodion BP 2000, Salicylic Acid Collodion USP 24, Salicylic Acid and Sulphur Ointment BPC 1973, Salicylin-P (FM), Salimar-Bad L, Salisoap, Salisol, Salvyl, Salycad (FM), Same-Seb, Samexid (FM), Sanoclorofila, Sastid, Savex with PABA, Savex with Sunscreen, Scalpicin, Scalpicin Anti-Dandruff Anti-Itch, Scholl Corn & Callous Removal Liquid, Scholl Seal & Heal, Schwefel-Diasporal (FM), Sebasorb, Sebaveen, Sebaveen (FM), Sebcur/T, Sebex, Sebex-T, Sebitar, Sebo Concept D/A, Seboderm (FM), Seborrol, Sebulex, Sebutone, Sebutone (FM), Sepso (FM), Sevorex, Simpsons, Soov Prickly Heat, Sophtal, St James Balm, Sterex, StieLasan (FM), Stiedex, Stiproxal, Stom-Antiba (FM), Stomyteol (FM), Stri-Dex Pads, Sucadermil, Sudermin (FM), Sudosin, Sulfo-Salicyl, Sulfoform (FM), Sulsal (FM), Superfade, Synthol, Synthol (FM), T/Gel, TCP, Tardan, Targel SA, Tarisdin, Tarlene, Tarpaste (FM), Tarsum, Tercinol (FM), Termobalsamo (FM), Termosan, Terradermina, Tersac, Therac, Theranyl, Therops (FM), Thrombo-Enelbin N (FM), Tiacid, Tintorine, Tinver, Tioderma (FM), Tirakallos, Toepedo, Topicorten-Tar, Topisalen, Topisalen (FM), Topisolon, Topisolon mit Salicylsaure, Trafuril (FM), Trigon Tintura (FM), U-Lactin Foot Cream, Ultralan-crinale (FM), Undetin (FM), Unguento Callicida Naion, Vartmedel (FM), Verel, Verra-med, Verrex (FM), Verrucare, Verrufilm, Verrumal, Verrupan, Verrusol (FM), Verrux, Versiclear, Vertebralon N, Verucid, Verufil, Verunec 3, Vipsogal, Viranol (FM), Viron Wart Lotion, Visotone, Volon A Tinktur, Volon A Tinktur N, W-Tropfen, Warondo Ekzemsalbe (FM), Warondo Psoriasissalbe (FM), Warondo-Flechtensalbe (FM), Warondo-Wundsalbe (FM), Wart-Off (FM), Wartkil (FM), Warz-ab Extor, Warzen-Alldahin, White Ointment USP 24, Whitfield Plus, Whitfields (Benzoic Acid Compound) Ointment, Whitfields Ointment, Wicne, Wicnelact, X-Seb Plus, X-Seb T, X-Seb T Plus, X-Tar, Xilorroidal (FM), Zeniac LP Fort, Zeta-Foot (FM), Zinc Oxide and Salicylic Acid Paste USP 24, Zinc and Salicylic Acid Paste BP 2000, Zinkosalb

CITIZENS PETITION

TO AMEND THE TFM FOR

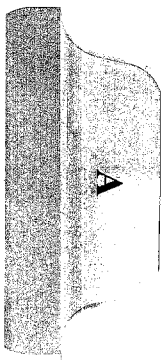
HEALTH CARE ANTISEPTIC DRUG PRODUCTS

TO INCLUDE **SALICYLIC ACID** AS A CATEGORY I INGREDIENT

BINDER 1 OF 1

APPENDICES A – G

COPY #1 OF 4 COPIES



INCI Name : Salicylic Acid
Chemical Name : Salicylic Acid

Colipa : P 14
EU : Annex VI, 1 – Nr. 3

SUBMISSION I

date : May 2000

TABLE OF CONTENTS

SUMMARY

This dossier addresses the safety of salicylic acid in cosmetic leave-on formulations (face and general cream) and rinse-off products (make-up removers, shower gels, shampoos and hair conditioners) at a level of 2%, leave-on hair care products at 1 % salicylic acid as well as the use of 0.5% salicylic acid as preservative in other cosmetic products.

Such products have a long history of use in both the EU and the US with no significant reports of dermal or acute effects. A safety assessment under worst-case exposure conditions shows that the use of such products provides a sufficient margin of safety with regard to systemic and reproductive effects.

Topical exposure

Exposure scenarios for consumer use of salicylic containing cosmetic products have been described in Attachment I.

For the worst-case exposure scenario, it has been estimated that the total consumer exposure to salicylic acid is 165 mg/day (topical exposure) resulting from the concomitant daily use of :

- ✓ a 2% salicylic acid-containing face cream,
- ✓ a 2% salicylic acid-containing general (hand) cream,
- ✓ a 1 % salicylic acid-containing leave-on hair product,
- ✓ rinse-off products (make-up removers, shower gels, shampoos and hair conditioners) containing 2% salicylic acid
- ✓ all other cosmetic products containing 0.5% salicylic acid.

In a more realistic but still exaggerated exposure scenario, it has been estimated that the total consumer exposure to salicylic acid is 125 mg/day (topical exposure) resulting from the daily use of :

- ✓ a 2% salicylic acid-containing general (hand) cream,
- ✓ all other cosmetic products containing 0.5% salicylic acid.

The serum levels relative to this topical exposure to salicylic acid have been estimated as 0.25 mg/100 ml.

Special considerations

To date, there are not many published studies which examine the toxicity of salicylic acid. There is, however, information on acetylsalicylic acid (aspirin) related toxicity following oral administration. Given the metabolic profile of orally absorbed acetylsalicylic acid and its rapid hydrolysis to salicylic acid, the available data concerning acetylsalicylic acid has been judged to have some relevance for salicylic acid. Therefore, in this dossier, studies conducted with acetylsalicylic acid have been used to address several toxicological endpoints. However, it should be considered that clinically salicylic acid is often considered ineffective when compared to acetylsalicylic acid.

The clinical inefficiency of salicylic acid when compared to acetylsalicylic acid is in agreement with the different mechanism of action postulated for acetylated versus non-acetylated salicylates. Pharmacokinetic studies have shown that although both, acetylsalicylic acid and salicylic acid, are able to inhibit prostaglandin synthesis by interacting with cyclo-oxygenase, the mechanism of action is different for acetylated and for non-acetylated salicylates. Acetylsalicylic acid inhibits prostaglandin synthesis by irreversible acetylation of the cyclo-oxygenase, whereas the interaction of salicylic acid with the cyclo-oxygenase is transient and reversible, and only minimally inhibits its activity. Similar differences have been observed for their effects on the alteration of bleeding times or

anticoagulant activity, which has been postulated to be the result of platelet dysfunction. Importantly, non-acetylated salicylates, such as salicylic acid, have only limited and transitory effects on platelet function, as opposed to the prolonged alteration caused by acetylsalicylic acid. These reversible effects on platelet function of non-acetylated salicylates could explain their inefficiency in increasing bleeding times when compared to acetylsalicylic acid. For example, laboratory studies have demonstrated that non-acetylated salicylates are at least 10 (*in vitro*) to 60-fold (*in vivo*) less effective in increasing bleeding times than acetylsalicylic acid. Interestingly, non-acetylated salicylates have been proposed as the preferred compounds for treatment if therapy is needed prior to surgery or in patients at risk for bleeding.

Therefore, based on the different pharmacokinetic activity between acetylated and non-acetylated salicylates, margins of safety calculated for certain endpoints in this dossier for which acetylsalicylic acid data are used, should be considered very conservative. It is also important to emphasize that, in most cases, the margins of safety have been calculated versus actual human data obtained from extensive clinical studies on the most sensitive population, which therefore require no interspecies or intraspecies correction factors.

Acute toxicity

The oral median dose (LD50) for salicylic acid has been reported as 400-3700 mg/kg in rats. However, when several 2% salicylic acid-containing products were administered to rats, the LD50 was estimated as greater than 10g/kg.

The dermal median lethal dose of salicylic acid has been reported as higher than 2 g/kg.

Based on the results of animal studies, formulations containing 2% salicylic acid carry minimal risk of eliciting serious acute ocular damage as a result of direct eye exposure to the product.

Skin toxicity

The skin irritation potential of salicylic acid has been evaluated in animal studies. Product formulations or alcohol solutions containing up to 5% salicylic acid with pHs between 2.3 and 3.0 cause minimal to no irritation to guinea pig skin after repeated open application for up to 5 days. When applied under occlusive or semi-occlusive conditions for up to 24 hours, formulations or alcohol solutions containing 2% salicylic acid with pHs between 2.8 and 4.0 cause minimal to no irritation to rabbit skin. In repeated application clinical studies, formulations containing up to 2% salicylic acid have been shown to be mild transient irritants and the skin effects observed do not differ significantly from those seen with products which do not contain salicylic acid. Under the conditions of use in the market place, these products have demonstrated to have a low potential for skin irritation.

There is no evidence that salicylic acid causes skin sensitization by skin contact. Based on the lack of response to skin prick challenge by salicylate-sensitive individuals and the lack of sensitization potential of salicylic acid, there is no significant risk of hypersensitivity reactions following topical administration of 2% salicylic acid containing formulations.

Repeated topical application of salicylic acid at concentrations up to 12% did not enhance the proliferative rate of basal cells measured as incorporation of ^{3}H-thymidine. Therefore, under the conditions of consumer exposure anticipated for topical products containing 2% salicylic acid, there appears to be minimal risk of eliciting clinically significant alterations in epidermal homeostasis.

Systemic toxicity

Subchronic percutaneous toxicity studies in rabbits have shown that the effect of salicylic acid up to 120 mg/kg/day (the highest dose tested) was limited to dermal irritation. This exposure is 41 times higher than the expected exposure to salicylic acid from the worst-case consumer scenario. In humans, severe salicylism by the dermal route is rare and normally associated with diseased state of the skin compounded by multiple application to large areas of the body, such as application of 6% salicylic acid topically six times per day to psoriatic patients over as much as 25% of the body surface area. Plasma salicylate levels required for systemic effects range between 46 and 64 mg/100 ml over a course of 3-10 days. These levels are at least 128 times higher than those estimated from topical application of cosmetic products containing salicylic acid of 0.36 mg/100 ml.

Teratogenicity

In monkeys, a NOEL of 100 mg/kg/day has been reported for acetylsalicylate-related teratogenic effects. The exposure from salicylic acid-containing cosmetic products under the worst-case scenario conditions (i.e. 2.96 mg/kg/day) is therefore 169 times lower than the reported NOEL in the monkey studies. Although salicylates are teratogenic in animal studies at relatively high levels of exposure, there is no solid evidence to link ingestion of normal therapeutic doses of salicylates to teratogenic events in humans. At low therapeutic doses (60-150 mg/day), large prospective studies have found no evidence that acetylsalicylic acid consumption during pregnancy leads to congenital malformations or the appearance of ductus artheriosus. These oral low therapeutic doses are estimated to result in serum levels up to 0.93 mg/100 ml which are higher than those estimated for the exposure to salicylic acid-containing cosmetic products under the worst-case scenario of 0.36 mg/100 ml. Importantly, these human data have been obtained in clinical studies conducted with acetylsalicylic acid. Considering the reversible activity of salicylic acid in inhibiting the prostaglandin synthesis and its clinical inefficiency when compared to acetylsalicylic acid, this margin of safety should be considered very conservative.

Mutagenicity/carcinogenicity

There are conflicting reports for the *in vitro* genotoxic potential of salicylic acid and acetylsalicylic acid. However, the results from mutation tests for both salicylic acid and acetylsalicylic acid generally have been negative under the relevant conditions of metabolic activation. Importantly, beyond the *in vitro* tests, carcinogen bioassay data for acetylsalicylic acid were negative and provides compelling overriding support that salicylic acid is not a carcinogen.

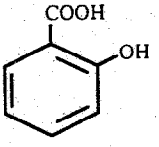
INTRODUCTION

Salicylic acid is a crystalline, white powder that was originally introduced for oral therapeutic purposes by Rev. Edmund Stone in 1763, who had observed that willow bark extract was effective against fevers. Free salicylic acid is also produced by microbes such as some *Actinomycetes*, the bacteria, *Aerobacter aerogens*, and the fungus, *Penicillium griseofulvum*. Hence, it has been identified as a component of fulvic and humic acids contained in natural waters and soil. Salicylic acid occurs commonly in fruits such as apples, oranges, plums and grapes. A synthetic process for mass production of salicylic acid became available in the mid 1800s. Salicylic acid and its derivatives are now widely used as analgesics, antipyretics, keratolytics, rubefacients, and anti-inflammatory agents.

The most widespread use of salicylic acid as a topical preparation is for the treatment of warts and corns, which makes use of the keratolytic activity of the material (Bart *et al.*, 1989; Steele *et al.*, 1988). For warts and corns, it is usually used in concentrations in excess of 12% and is often formulated in paints, films or adhesive plasters (Bunnney *et al.*, 1976). Salicylic acid used in a cream up to 6% is an effective treatment of ichthyosis, psoriasis and hyperkeratotic eczema (Elie *et al.*, 1983). It is also used in combination creams with dithranol, tar and corticosteroids to enhance penetration of the active drug.

At levels up to 2 %, salicylic acid is used in cosmetics since decades as preservative and in products which use its exfoliating and skin cleansing properties.

1. GENERAL DATA

Chemical Name:	Salicylic acid
Synonyms:	O-Hydroxybenzoic acid, 2-Hydroxybenzoic acid
CAS Registry Number:	69-72-7
Chemical configuration:	
Molecular Formula:	C7H6O3
Molecular Weight	138.12
Specifications:	
Melting Point:	158-160 °C
Boiling Point:	211 °C at 20 mmHg
Vapor Pressure:	5 mmHg at 136 °C
Density:	1.443 at 20 °C
Partition Coefficient:	Log Pow: 0.35
Solubility in Water:	2.17 mg/ml at 20 °C
Solubility Other Solvents:	Ethanol, Diethyl ether
Flash Point:	157 °C
Fields of Application:	
Food	As preservative
Dye/other salicylate	Raw material for manufacture
Chemistry	Analytical reagent
Medicine	Topical keratolytic (0.5-12%)
Veterinary	Antiseptic and antifungal by topical application
Cosmetics	Preservative, active ingredient in skin-cleaning and exfoliating products (0.2-2%)
Natural Occurrence:	Wintergreen leaves, willow and sweet birch bark, bacteria, fungi and fruits.

2. METABOLISM, PHARMACOLOGY AND PHARMACOKINETICS

2.1. Metabolism

Animal

Salicylic acid and derivatives are weak acids, therefore following oral administration, almost all salicylate is found in the unionized form in the stomach. Acetylsalicylic acid is poorly soluble in the acid media of the stomach and precipitates may coalesce to form concretions, thereby delaying the absorption for 8 to 24 hours. Despite the higher pH of the small bowel, the larger surface area allows absorption of salicylate and this occurs rapidly at therapeutic doses. However absorption following overdose commonly occurs more slowly and blood concentrations can continue to rise for up to 24 hours after ingestion (Ferguson & Boutros, 1970; Kaufman & Dubanksy, 1972; Levy, 1978).

About 50-80 % of salicylate in the blood is bound by protein while the rest remain in the active, ionized state. Protein binding is concentration dependent, so saturation of the binding site leads to more free salicylic acid and increased toxicity. The volume of distribution is 0.1-0.2 L/kg. Acidosis increases the volume of distribution because of enhancement of tissue penetration of salicylates (Levy & Tsuchiya, 1972). Acetylsalicylic acid is hydrolyzed in the stomach and in the blood to salicylic acid and acetic acid. The biological half-life of acetylsalicylic acid is only 20 minutes. On the other hand, the plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, whereas in overdose this increases to 18 to 36 hours (Done, 1960).

Approximately 80% of a small dose of acetylsalicylic acid is metabolized in the liver. Conjugation with glycine forms salicyluric acid and with glucuronic acid forms salicyl acyl and phenolic glucuronide. Small amounts of salicylic acid are also hydroxylated to gentisic acid. These metabolic pathways have only a limited capacity (Levy & Tsuchiva, 1972).

Salicylates are excreted mainly by the kidney as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%) and acyl (5%) glucuronides and gentisic acid (< 1%). When small doses (less than 250 mg in an adults) are ingested, all pathways proceed by first order kinetics, with an elimination half-life of about 2-3 hours (Hartwig-Otto, 1983). When higher doses of salicylate are ingested (more than 4 g), the half-life becomes longer (15-30 hours) because the biotransformation pathways concerned with the formation of salicyluric acid and salicyl phenolic glucuronide become saturated and the kinetics switch from first to zero order (Levy & Tsuchiva, 1972). Renal excretion of salicylic acid becomes increasingly important as the metabolic pathways becomes saturated because it is extremely sensitive to changes in urinary pH above 6.0. The use of urinary alkalization exploits this particular aspect of salicylate elimination.

Human

Metabolism of acetylsalicylic acid has been studied in humans. Ingested acetylsalicylic acid is mainly absorbed as such, but some enters the systemic circulation as salicylic acid, because of hydrolysis by esterases in the GI mucose and liver. Acetylsalicylic acid can be detected in plasma only for a short time as a result of hydrolysis in plasma, liver and erythrocytes. After ingestion of a 0.6 g dose, acetylsalicylic acid could only be detected for 30 minutes since only 27% of the total plasma salicylate was found to be acetylated (Gilman *et al.*, 1990). As a result, plasma concentrations of acetylsalicylic acid are always low and rarely exceed 20 µg/ml at ordinary therapeutic doses. After absorption, salicylate is rapidly distributed throughout most body tissues and most transcellular fluids, primarily by pH-dependent passive processes. It can be detected in spinal and peritoneal fluid, saliva, milk and cerebrospinal fluid (Gilman *et al.*, 1990).

In a study in which 10 human volunteers took a therapeutic dose of acetylsalicylic acid (600 mg) by mouth and 9 patients took acetylsalicylic acid overdose, salicyluric acid was the major urinary metabolite in volunteers (63%), whereas salicyluric (30%) and salicylic acid (34%) were the main ones for the overdose patients. The study showed that the excretion of salicyluric acid decreased with

increasing doses, whereas gentisic acid and salicyl phenolic and acyl glucuronides increased. The profile of acetylsalicylic acid elimination was qualitatively similar in man and rat, but there were quantitative differences. Limited capability to form salicyluric acid was observed in both species, however, dependence of this pathway in rat was low and compensated by other elimination routes whereas in man the dependence on this pathway was high, and in overdose, compensation by other routes was incomplete (Patel *et al.*, 1990).

A similar elimination pattern was found in another study in which following oral administration of 1 g of acetylsalicylic acid in man, 10% of the total urinary salicylate was salicylate itself, 70% was salicyluric acid and 20% appeared as glucuronides. Salicylic acid levels in urine was up to 3% in patients whose urinary pH was 5-5.6, but were increased to up to 25% for urinary pHs between 6.0 and 7.0 (LaDu *et al.*, 1971).

Because of the differences in metabolism, it may be postulated that the toxicity observed from high doses of acetylsalicylic acid is not relevant for the low level of exposure to salicylic acid from cosmetics.

2.2. Pharmacology/Pharmacokinetics

Human

Salicylic acid and its derivatives are widely used as analgesics, antipyretics, keratolytics, rubefacients and anti-inflammatory agents. Whether salicylates are administered orally, rectally, intravenously or percutaneously, in all cases systemic absorption occurs.

The exact mechanism for all pharmacological effects of salicylate have not been established but appear to be linked, in part, to the inhibition of prostaglandin synthesis. Acetylsalicylic acid inhibits the synthesis of prostaglandins by irreversible acetylation of the cyclo-oxygenase enzyme which is critical to the synthesis of prostaglandins from arachidonic acid.

Whilst salicylic acid also interacts with the cyclo-oxygenase, it only minimally inhibits its activity. Thus, prostaglandin synthesis inhibition by non-acetylated salicylate appears to also involve other mechanisms. For example, salicylate does not inhibit the formation of 12-hydroperoxyarachidonic acid (12-HPETE) and leukotrienes from arachidonic acid. Cyclo-oxygenase and lipoxygenase appear to compete for arachidonic acid and thus, the inhibition of cyclo-oxygenase by salicylate may result from the transient increase in the formation of 12-HPETE and leukotrienes and a obligatory decrease in cyclo-oxygenase activity.

Salicylic acid exerts its dermatological activity only when applied topically and in its free acid form. According to Weirich (1975), when applied in low concentrations (equal or below 0.3% w/w), salicylic acid exerts a germistatic effect on the skin. At concentrations of 0.1% (w/w), it exerts an acidogenic effect on the skin surface. When salicylic acid is applied at concentrations of 1-4% (w/w), it displays a keratin dispersing (softening) and surface-keratolytic effect. The keratolytic effect of salicylic acid is dose-dependent and concentrations of 5% or greater decrease intracellular cohesion between corneocytes in the stratum corneum, resulting in increased shedding (corneolysis) (Huber and Christophers, 1977; Roberts *et al.*, 1980). The mechanism responsible for desquamation appears to be the solubilization of proteins, including glycoproteins (Goldsmith, 1979).

Once absorbed, salicylates are rapidly distributed throughout the extracellular fluid and most tissues. High concentrations occur in the liver and kidney. Albumin and other plasma proteins can bind up to 50-80% of salicylic acid in plasma and it is only the free drug which exerts pharmacological activity. In conditions associated with decreased plasma albumin, the total concentration of salicylic acid in blood can be relatively low, however more of the drug can be in the free state and thereby concentrated in the tissues. This is the case in young children (less than 10 years old) where the plasma albumin level is relatively low. Exposures to relatively low doses can lead to toxicity because there is more unbound salicylate in the serum. The apparent volume of distribution of salicylate at

usual therapeutic doses is 150-200 mg/kg, but may be higher in neonates. The volume of distribution appears to increase with increasing dose and/or increasing serum salicylate concentrations or as stated previously in conditions of decreased serum albumin.

Biotransformation of salicylate takes place mainly in the hepatic endoplasmic reticulum and mitochondria. Salicylic acid is removed from the body by five parallel and competing pathways: renal excretion, conjugation with glycine, conjugation of the carboxy or phenolic group to form a glucuronide and hydroxylation to form gentisic acid. Two of these pathways (liver conjugation to salicylic acid and the phenolic glucuronide) are easily saturable and thus the steady-state amount of salicylic acid in the body increases proportionately with increasing dose rates. The plasma half-life for salicylate is 2 to 3 hours at normal therapeutic doses and about 12 hours at anti-inflammatory doses for treatment of rheunatic arthritis, etc. Moreover, the half-life of salicylate may be as long as 15 to 30 hours at high therapeutic doses or in situations of intoxication (Gilman *et al.*, 1990).

To better understand salicylic acid pharmacokinetics following use in topical preparations, a clinical pharmacokinetic study has been conducted to determine systemic salicylic acid burden after topical use of a leave-on 2%-salicylic acid-containing cosmetic product and to compare this to the circulatory levels of salicylate achieved after ingestion of a benchmark dose of acetylsalicylic acid. The study evaluated the percutaneous absorption of salicylic acid from two leave-on formulations, one of which was formulated in a hydroalcoholic vehicle and another formulated as a non-hydroalcoholic cream, and the gastric absorption of a baby acetylsalicylic acid (81 mg). Serum and urine salicylate levels were collected from subjects that received topical application of either formulation to their face and neck. Subjects were divided into three groups based on skin type (photoaged, acnegenic and normal) as defined by dermatological examination. The subjects received one dose of either formulation (a minimum of 1.25 g to a maximum of 1.5 g of the 2% salicylic acid-containing formulation; equivalent to approximately 25 mg of salicylic acid) per day for a total of 16 days. There was a total of 40 subjects who received topical application of either formulation. Twenty subjects had normal skin, ten subjects had acnegenic skin and ten subjects had photoaged skin. Ten of the twenty subjects with normal skin and the subjects with acnegenic skin received daily application of the hydroalcoholic formulation. The remaining ten subjects with normal skin and the subjects with photoaged skin received the cream formulation. Included in the study for comparative purposes was a fourth subject group (12 subjects) who received one daily dose of Bayer Children Chewable Acetylsalicylic acid (81 mg) for a total of 16 days and no topical application of any of the 2% salicylic acid-containing formulation. The serum salicylate data obtained in this study are given in the tables 1 and 2.

Table 1: Daily pre-dosing plasma salicylate levels in subjects treated daily with topical or oral salicylic acid[a]

		Plasma salicylate levels (µg/L)			
Facial Skin	**Vehicle type**	**Day 7**	**Day 12**	**Day 15**	**Day 16**
Normal	Cream	36.1 ± 21.3	14.4 ± 2.2	23.7 ± 8.1	29.5 ± 7.0
Normal	Hydroalcoholic	52.1 ± 13.1	44.0 ± 8.3	40.3 ± 7.9	41.7 ± 6.5
Aged	Cream	36.4 ± 5.6	38.1 ± 9.9	29.3 ± 11.6	21.6 ± 4.9
Acnegenic	Hydroalcoholic	60.8 ± 21.3	43.6 ± 13.1	35.6 ± 9.9	34.6 ± 6.4
N/A	Oral aspirin	< 10.0	< 5.0	< 10.0	< 10.0

[a] *Data presented are the Mean ± SEM of 9-10 subjects in each treatment group.*

On each day of the study, resting (pre-dosing) salicylate levels were slightly higher in subjects receiving topical treatment compared to oral ingestion. However, within the groups receiving the topical treatment, resting salicylate levels remained at steady-state between days 7 and 16. The peak salicylate levels for topically treated subjects were 1/20th and 1/10th those seen in subjects receiving oral acetylsalicylic acid, respectively. In a similar vein, total systemic exposure (measured as the 24

hour area under the curve values) in subjects treated with the cream product was 1/8th of that seen in subjects receiving oral acetylsalicylic acid, whereas the subjects receiving the hydroalcoholic formulation showed a total systemic exposure of 1/5th that of the oral treatment group. Neither area under the curve, nor the peak salicylate levels were affected by the skin type although both parameters achieved higher levels with the hydroalcoholic formulation when compared to the cream product. Likewise, peak plasma levels were achieved faster with the hydroalcoholic formulation compared to the cream vehicle. Overall, the data demonstrated that the systemic burden resulting from topical application of a 2% containing formulation is well below that achieved via the administration of one baby aspirin. The data supports that percutaneous absorption of salicylic acid from topically applied 2% salicylic acid containing products is in the range of 20% of the applied dose (Procter & Gamble, 1994f; Davis, 1997).

Table 2: Steady state plasma pharmacokinetic parameters

Skin Type	Vehicle	Peak plasma level (μg/L)	Time to peak levels (hrs)	AUC levels (μg hrs/L)
Normal	Cream	293 ± 37[a]	4.3 ± 0.4	3108 ± 293
Aged	Cream	275 ± 58	4.11 ± 0.6	2636 ± 302
Normal	Hydroalcoholic	525 ± 66[b]	1.89 ± 0.35	4225 ± 425[b]
Acnegenic	Hydroalcoholic	487 ± 41	1.67 ± 0.2	3893 ± 329
N/A	Oral aspirin	5282 ± 457[c]	0.71 ± 0.2	22010 ± 3907

AUC: Area Under the Curve. [a] Data presented are the mean ± SEM for 9-10 subjects in each treatment group. [b] Significantly different from subjects presenting normal facial skin treatment with 2% salicylic acid in a cream vehicle. [c] Statistically different from all topical treatments.

Conclusion

Whether salicylates are administered orally, rectally, intravenously or percutaneously, in all cases systemic absorption occurs. Given the metabolic profile of orally absorbed acetylsalicylic acid and its rapid hydrolysis to salicylic acid, the available data concerning acetylsalicylic acid has been judged to have some relevance for salicylic acid. However, it should be considered that clinically salicylic acid is often considered ineffective when compared to acetylsalicylic acid. The clinical inefficiency of salicylic acid when compared to acetylsalicylic acid is in agreement with the different mechanism of action postulated for acetylated versus non-acetylated salicylates. Pharmacokinetic studies have shown that although both, acetylsalicylic acid and salicylic acid, are able to inhibit prostaglandin synthesis by interacting with cyclo-oxygenase, the mechanism of action is different for acetylated and for non-acetylated salicylates. Acetylsalicylic acid inhibits prostaglandin synthesis by irreversible acetylation of the cyclo-oxygenase, whereas the interaction of salicylic acid with the cyclo-oxygenase is transient and reversible, and only minimally inhibits its activity. The peak salicylate levels for subjects treated topically with a 2% salicylic acid containing formulation were between 1/10th to 1/20th those seen in subjects receiving acetylsalicylic acid (81 mg) orally. Overall, systemic burden resulting from topical application of a 2% containing formulation is well below that achieved via the administration of one baby aspirin.

3. ANIMAL TOXICOLOGY AND HUMAN DATA

3.1. SINGLE EXPOSURE

3.1.1. Acute toxicity

Acute oral toxicity

Animal

The oral LD50 for salicylic acid has been estimated as 400-891 mg/kg in rats (McCann *et al.*, 1975; BIOFAX, 1971). Studies have also been conducted to evaluate the LD50 of formulations containing salicylic acid in rats. Results from these tests show that the LD50 of the formulations, ranging from 10 to 20 g/kg, were not modified by the presence of salicylic acid up to 2% in final product (Procter & Gamble, 1989a, 1993a, 1993b).

Human

The mean oral lethal dose of sodium salicylate and derivatives has been estimated between 20 and 30 g in adults (Goodman and Gilman, 1970). Toxic effects usually appear whenever 10 g or more of salicylates are ingested in single or divided doses over a period of 12 to 24 hours (Dubow and Soloman, 1948). Children, especially under the age of 3 years, are more susceptible than adults to the toxic action of salicylates.

Acute dermal toxicity

Animal

The acute dermal toxicity of salicylic acid has been evaluated in rabbits. No signs of erythema and oedema were observed after topical application of a salicylic acid solution at a dosage of 2 g/kg to the intact or the abraded skin of rabbit (Procter & Gamble, 1976b). From this study, it was concluded that the dermal LD50 for salicylate was greater than 2g/kg in rabbits.

Conclusion

The oral median dose (LD50) for salicylic acid has been reported as 400-3700 mg/kg in rats. However, when several 2% salicylic acid-containing products were administered to rats, the LD50 was estimated as greater than 10g/kg. The dermal median lethal dose of salicylic acid has been reported as higher than 2 g/kg.

3.1.2. Skin irritation

Animal

Several non-clinical tests have been conducted with alcohol solutions and other cosmetic formulations containing salicylic acid. A summary of the results of these tests is shown in table 3.

The effects of alcoholic solutions containing 2% salicylic acid applied under occlusive conditions for 24 hours to the intact and abraded skin of rabbits have been evaluated (Procter & Gamble, 1979a). The test material elicited minimal irritation with a primary irritation index (P.I.I.) of 0.3. Slight to moderate erythema (grades 0.5-2.5) was observed at the 24 hours reading. No oedema was present at the 72 hour observation.

Conclusion

The skin irritation potential of salicylic acid has been evaluated in rabbits. Product formulations or alcohol solutions containing up to 2% salicylic acid with pHs between 2.8 and 4.0 cause minimal to no irritation to rabbit skin when applied under occlusive or semi-occlusive conditions for up to 24 hours.

Table 3: Skin irritation studies

Test type	Test material	Test conditions	Results	Reference
Patch Tests				
Primary skin irritation (rabbits)	• LA[2]/NI% SA, pH 4.0	0.5 g, semi-occlusive patch for 4 hours	Moderately irritating (P.I.I. = 2.5)	P&G, 1995a
Primary skin irritation (rabbits)	• 2% SA in alcohol solution, pH 2.65	0.5 g, occluded patch for 24 hours	Minimally irritating	P&G, 1979a
Primary skin irritation (rabbits)	• 2% SA in alcohol solution, pH NI	0.5 ml, occluded patch for 24 hours	Non-irritating	P&G, 1980
Primary skin irritation (rabbits)	• HC[1]/0.25% SA, pH NI • HC[1]/0.5% SA, pH 2.81	0.5 ml, occluded patch for 24 hours	Non-irritating	P&G, 1982c

SA: Salicylic acid..[1] HC: Hydroalcoholic cleanser. [2] LA: Laundry Additive. [3] NI: Not Indicated. [4]P.I.I.: Primary Irritation Index.

3.1.3. Eye irritation

Animal

The *in vivo* eye irritation potential of several formulations containing salicylic acid has been evaluated in a modified Draize test called the Low Volume Eye Test (LVET) and the results have been summarized in table 4. In the LVET, 0.01 ml volume of the test material is applied to the central cornea of the rabbit eye and the effects on ocular tissues (cornea, conjunctiva and iris) are graded using a scoring scale (Griffith *et al.*, 1980). The readings are made until responses are cleared. The individual tissue grades are usually weighted and combined into a Maximum Average Score (MAS; 0 to 110 scale), which gives an indication of the average level of response on the day of the highest average reading. The rate of reversal of rabbit eye responses is reported as median days to clear.

The maximal average score (MAS) of the tested formulations varied between 0 and 6.3 and the corresponding median days to clear ranged between 0 and 4. These data characterize salicylic acid containing materials, which elicit MAS scores less than 10 with up to 4 days to clear, as mild irritants.

Human

The eye irritation potential of formulations containing salicylic acid have been evaluated in human volunteers in several studies. In a study which involved a single periocular application of a cosmetic cream containing 2.0% salicylic acid, transient subjective irritation (stinging, burning, itching and foreign body sensation) was observed in some of the volunteers. There were ophthalmic findings of mild to moderate palpebral conjunctival inflammation and mild bulbar conjunctival inflammation which were temporary. Evaluation of subjects corneas revealed a fluorescein staining pattern of mild to moderate corneal superficial punctuate keratopathy. The irritation resolved in all volunteers within 96 hours. In this study, it was also demonstrated that this cream, when applied to the periocular area could migrate into the eye (Procter & Gamble, 1995h). A second study involved twice daily applications for five days of the 2.0% salicylic acid containing cream to normal and sensitive eye volunteers (Procter and Gamble, 1996b). Ocular effects observed in this study involved mild to moderate bulbar conjunctival inflammation and the induction of mild to moderate corneal superficial punctuate keratopathy as indicated by fluorescein staining. Irritation did increase with increasing length of exposure to the cream in this study. All eyes returned to normal within two days after cessation of exposure to this cream.

The 2.0% cream used in the above described studies was reformulated to incorporate a different solvent system and a reduction in salicylic acid from 2.0% to 1.5% salicylic acid (pH of 2.5-2.8). The ocular irritancy of the reformulated product was evaluated in a 3 day periocular study. Under the conditions of this study, the test formulation elicited no reports of subjective irritation (stinging, burning, itching, dryness and/or foreign body sensation). There were ophthalmic findings of mild conjunctival inflammation and mild or no superficial corneal punctate keratopathy in subjects using the salicylic acid containing formulation. The ocular involvement was temporary in nature as confirmed in follow-up examinations of these subjects (Procter & Gamble, 1995g,h). The test material was less irritating than the 2.0% cream used in the previous studies. The mild eye irritancy of this formulation was confirmed in a 4 week safety in use study (discussed below).

A 4 week safety-in-use study was conducted with two 1.5% salicylic acid containing and two non salicylic acid containing cosmetic creams. Subjects were asked to apply the cosmetic product around the eyes (i.e. under the eye and on the corner of the eye but not on upper eyelids) at least 2 times per day for 28 days. Standard ophthalmological exams were conducted prior to product use and at 14 and 28 days of product use during the study. Results from this study indicated findings of mild ocular irritation and the incidence of objective and subjective eye experiences (stinging, burning, itching, dryness) were not significantly different across the different formulations. (Procter and Gamble, 1996). A 14 day safety- in-use study was conducted with 1.5% salicylic acid containing cosmetic

creams and a cream containing no salicylic acid in subjects with dry eyes. Subjects were asked to apply the products evenly over the face and eyes including eyelids at least once daily. No reports of subjective adverse ocular reactions associated with product use occurred. Superficial conjunctival and corneal fluoroscein staining scores were mild and similar across the different formulation types (Procter & Gamble 1995z).

A 6 week home use test was conducted with cosmetic formulations containing up to 2.0% salicylic acid and a pH of 3.0-3.09 formulations. A total of 112 subjects (64 users of salicylic acid containing products and 58 users of the control products without salicylic acid) were evaluated for ophthalmological effects. Mild irritation to the eyes was experienced by 7 subjects, 4 of which used a product containing salicylic acid. Ophthalmological findings were typically mild, transient and/or sporadic with equivalent low level of occurrence in salicylic acid or non salicylic containing formulations (Procter & Gamble, 1995i).

Conclusion

Based on the results of the animal studies, formulations containing up to 2% salicylic acid carry minimal risk of eliciting serious acute ocular damage as a result of direct eye exposure to the product. In humans, formulations containing up to 2% salicylic acid applied periocularly have the potential to cause mild ocular irritation. This irritation involves superficial effects to the conjunctiva and cornea that are reversible. The level of eye irritation observed with salicylic acid containing cosmetic formulation is significantly influenced by the matrix composition and the ability of the matrix to migrate into the eyes.

Table 4: Low Volume Eye Tests[1]

Test type	Test material	MAS	Median days to clear	Comments	Reference
LVET	NH cleansing milk with 0.05% SA, pH 5.4	2.7	1	Redness and discharge	P&G, 1996
	NH toner with 0.2% SA, pH 5.7	2.7	2	Redness and discharge	
LVET	NH moisturizer with 2% SA	5.3	4	Conjunctivitis	P&G, 1993c
LVET	Hydro gel with 2% SA	3.3	3	Conjunctivitis	P&G, 1993d
LVET	NH cleanser with 2% SA, pH 3.09	4.3	4	Iritis (1/3), conjunctivitis (2/3)	P&G, 1995b
	NH cleanser with 2% SA, pH 3.09	2.0	3	Conjunctivitis (2/3)	
	NH cleanser with 2% SA, pH 3.09	6.3	4	Iritis (1/3), conjunctivitis (3/3)	
LVET	NH moisturizer containing 2% SA	1.3	2	conjunctivitis (2/3)	P&G, 1993e
LVET	NH cream with 1.5% SA	2.7	3	Conjunctival swelling and redness (2/3)	P&G, 1995c
	NH cream with 1.5% SA	0.7	1	Conjunctivitis (1/3)	
	NH cream with 1% SA	0.7	1	Conjunctivitis (1/3)	
LVET	NH moisturizer with 2% SA, pH 2-3	2	2	Conjunctivitis (2/3)	P&G, 1994a
	NH moisturizer with 2% SA, pH 4-5	2	2	Conjunctivitis (2/3)	
LVET	NH moisturizer with 2% SA	0.7	1	Conjunctival redness (1/3)	P&G, 1995d
	NH moisturizer with 2% SA	1.3	1	Conjunctival redness and swelling (1/3)	
	NH moisturizer with 1.5% SA	2.0	3	Conjunctival redness (3/3)	
	NH moisturizer with 0.5% SA	0.0	0	No effects observed	
LVET	NH cream with 2% SA	3.3	2	Conjunctivitis (3/3)	P&G, 1995e
LVET	Hydro after-shave with 2% SA	1.3	4	Conjunctival discharge and redness (2/3)	P&G, 1995f
	Hydro after-shave no SA	1.3	2	Conjunctival redness (2/3)	

SA: Salicylic acid. MAS: Maximum Average Score. NH: Non-hydroalcoholic. Hydro: Hydroalcoholic

[1] *In the LVET, 0.01 ml volume of the test material is applied to the central cornea of the rabbit eye and the effects on ocular tissues (cornea, conjunctiva and iris) are graded using a scoring scale (Griffith et al., 1980). The individual tissue grades are usually weighted and combined into a Maximum Average Score (MAS; 0 to 110 scale), which gives an indication of the average level of response on the day of the highest average reading. The rate of reversal of rabbit eye responses is reported as median days to clear.*

3.1.4. Dermal penetration studies

Animal

Dermal penetration of salicylic acid from different vehicles has been evaluated in rabbits (Stolar *et al.*, 1960). Several ointment bases (hydrophilic ointment, hydrophilic petrolatum, petrolatum or polyethylene glycol) containing 6% salicylic acid were applied to the skin of New Zealand White rabbits at a dose of 7.5 g per animal. Peak blood levels (12 mg/100 ml plasma) of salicylic acid were observed at 4.5 hours after application of the hydrophilic ointment. The plasma levels were 8 mg/100 ml plasma at 6 hours for the hydrophilic petrolatum and 6.5 mg/100 ml at 4 hours with petrolatum. Salicylic acid was undetectable in plasma in the group treated with this material in propylene glycol over an 8 hour time course.

Goldsmith (1979) demonstrated that the addition of polyethylene glycol 400 or polyethylene glycol 6000 to aqueous solutions reduced the *in vivo* absorption of salicylic acid through intact skin.

Birmingham *et al.* (1979) studied the percutaneous absorption of salicylic acid in rabbits by applying 10 g of 10% salicylic acid in a hydrophilic ointment to the shaved backs of rabbits. Peak plasma levels were 10-18 mg/100 ml. The authors postulated that poor systemic absorption of salicylic acid in the presence of propylene glycol was due to the formation of a glycol-salicylate complex resulting in a molecule too large to pass through the stratum corneum.

The dermal penetration of salicylic acid from oily vehicles has been evaluated in guinea pigs by Washitake *et al.* (1975). Salicylic acid dissolved in liquid paraffin, isopropyl myristate, hexadecyl alcohol and oleic acid at concentrations of 75, 150 and 300 μg/ml was applied to the skin of guinea pigs. The percentage of salicylic acid absorbed was independent of the concentrations used over a period of 6 hours, but absorption varied between vehicles, with values of 14.6% for the liquid paraffin, 1.7% for the isopropyl myristate, 1.6% for the hexadecyl alcohol and 1.5% for the oleic acid vehicles.

Arita *et al.* (1970) demonstrated that a solution of salicylic acid at pH 3.0 was absorbed faster than the same solution at pH 4.0 when applied to the abdominal skin of guinea pigs. These authors postulated that absorption of salicylic acid occurs by simple diffusion and that the rate of salicylic acid absorption does not depend on the concentration applied after lapse of a certain initial time. The investigators concluded that salicylic acid in its unionized form has an increased dermal penetration.

Dermal penetration from occluded application of 1%, 5% and 10% salicylic acid in a hydrophilic ointment for 7.5 hours daily for 4 weeks to the skin of rats at a dosage of 0.67g/cm^2 was evaluated by Roberts & Horlock (1978). The average penetration of 5% and 10% salicylic acid was significantly lower at 4 weeks relative to that seen the first week. The penetration of the 1% salicylic acid-containing ointment remained constant over the course of the experiment. Histological observations of the skin treated with 5 and 10% salicylic acid preparations showed initial increases in the flux occurring after 2 days of treatment, corresponding with swelling and exfoliation. The authors proposed that skin dehydration after repeated application could be the reason for the decreased level of absorption.

The *in vitro* time course for cutaneous penetration of salicylic acid from two salicylic acid solutions and 4 product formulations was analyzed using the excised skin of human donors. Since the penetration of salicylic acid across the epidermal barrier is influenced by the vehicle in which it is applied, the study was designed to determine a permeability constant (Kp), a pseudo-steady-state rate of penetration and the percentage of salicylic acid that is absorbed from each formulation over time. Both hydroalcoholic and non-hydroalcoholic vehicles were included in the study. Results from this study indicated that dermal penetration from the hydroalcoholic vehicles was greater than from the non-hydroalcoholic vehicles. The following rank was obtained on the basis of the calculated Kp values of the 6 different test materials containing 2% salicylic acid (least to greatest): Propylene

glycol < Non-hydroalcoholic cream < Non-hydroalcoholic lotion < Hydroalcoholic gel < Ethanol (35%) < Hydroalcoholic stick (Procter & Gamble, 1994b).

Relevant data for the dermal penetration has been developed from measurements of steady state plasma levels after topical application of salicylic acid containing cosmetic formulations (see also 2.2. Pharmacokinetics). Plasma salicylate levels after daily topical exposure to 1.5 mg of hydroalcoholic product or cream containing 2 % of salicylic acid, were $1/5^{th}$ to $1/8^{th}$ of the levels after oral ingestion of a baby aspirin (Procter & Gamble 1994 f, Davis 1997).

Conclusion

In animal or *in vitro* studies, the percutaneous absorption of salicylic acid is dependent on vehicle of application, pH, skin hydration, number of applications and skin condition. Based upon the data of the numerous studies, salicylic acid dermal penetration occurs readily when dissolved in a hydrophilic ointment. The inclusion of certain polymers in the formulation may be used to decrease the dermal penetration of salicylic acid. Depending on the formulation, percutaneous penetration can be as much as 20 %. Plasma salicylate levels after daily topical exposure to 1.5 mg of hydroalcoholic product or cream containing 2 % of salicylic acid, were $1/5^{th}$ to $1/8^{th}$ of the levels after oral ingestion of a baby aspirin.

3.2. REPEATED EXPOSURE

3.2.1. Skin Sensitization

Animal

Delayed contact hypersensitivity tests were conducted with salicylic acid and related materials such as methyl salicylate, acetyl salicylate and hexadienyl acetyl salicylate according to the modified Buehler test protocol (Robinson *et al.*, 1990). For the induction procedure, solutions in 80% ethanol of salicylic acid (25%, w/v), acetyl salicylate (25%, w/v), methyl salicylate (25%, w/v) or hexadienyl acetyl salicylate (25%, w/v) were applied topically to the intact skin of 20 guinea pigs. Patches were applied for 6 hours, once a week for a total of 3 weeks. After 2 weeks rest period, challenge was conducted using the same test material concentrations used for induction. The results from these studies showed that none of the above solutions were skin sensitizers (Procter & Gamble, 1975, 1976d, 1976e, 1976f).

Human

Immediate Type sensitivity reactions to acetylsalicylic acid occur only rarely, while sensitivity reactions to other salicylates are extremely rare. Importantly, individuals who are sensitive to orally ingested acetylsalicylic acid generally do not respond to skin prick challenge with salicylate (Settipane, 1983). Immediate Type sensitivity reactions seem to be of no relevance for topical application of salicylic acid containing cosmetics, based on the long history of safe use of such products in the market place.

With respect to delayed-type (Type IV) hypersensitivity, consensus that topically applied salicylic acid is not a contact allergen is provided in the literature (Cassano *et al.*, 1999, Nater & Groot, 1985; Rasmussen & Fisher, 1976). Moreover, many Human Repeated Insult Patch Tests (HRIPT) and cumulative tests have been conducted with formulations containing up to 2% salicylic acid. The results from these tests (table 5) show that there is no evidence that topical administration of salicylic acid-containing formulations causes skin sensitization.

Conclusion

Based on the lack of response to skin prick challenge by salicylate-sensitive individuals and the lack of sensitization potential of this ingredient with regard to delayed-type hypersensitivity, there seems to be no significant risk of hypersensitivity reactions following topical application of salicylic acid-containing formulations. This is confirmed by a long history of safe use of cosmetic products containing salicylic acid.

Table 5: HRIPTs conducted with formulations containing salicylic acid

Test material	Salicylic acid under patch (%)	pH	Patch type	Results	Reference
Hydroalcoholic lotion	0.5	NI	Occlusive	3/84**	P&G, 1988a
NH cream	1	2.87	NI	0/86	P&G, 1988b
Hydroalcoholic gel	0.5	NI	Occlusive	0/89	P&G, 1988c
Hydroalcoholic cleansing foam	0.5	4.5-5.0	Occlusive	0/101	P&G, 1989b
Hydroalcoholic cleanser	0.5	2.82	Occlusive	1/86*	P&G, 1993g
NH liquid make-up	0.55	NI	Occlusive	0/98	P&G, 1993h
Hydroalcoholic gel	2	NI	Occlusive	0/102	P&G, 1993I
NH cream	2	3.15	Occlusive	0/108	P&G, 1993j
NH moisturizer	2	3.17	Occlusive	0/99	P&G, 1993k
NH lotion	0.06	NI	Occlusive	0/113	P&G, 1995j
NH cleanser	0.3	NI	Semi-occlusive	0/99	P&G, 1995k
NH cleanser	0.3	3.0	Semi-occlusive	0/104	P&G, 1995l
NH cream	0.3	3.04	Semi-occlusive	0/105	P&G, 1995m
NH moisturizer	0.2	7.28	Occlusive	0/99	P&G, 1995n
NH moisturizer	1.5	NI	Occlusive	0/114	P&G, 1997
NH rinse-off product	NI	NI	Occlusive	0/25	J&J, 4
NH cleanser	0.02	NI	Occlusive	0/26	J&J, 5
NH cream	2	NI	Occlusive	0/178	J&J, 6
NH rinse-off product	0.08	NI	Occlusive	0/34	J&J, 7
NH cream	2	3.8	Occlusive	0/193	J&J, 8
NH cream	2	3.8	Occlusive	0/198	J&J, 9
NH cream	2	NI	Occlusive	0/101 (50% of the panellists with self-assessed sensitive skin)	P&G, 1993x
NH cream	2	2.6-2.7	Semi-occlusive	1/102*	P&G, 1994k

NI: Not indicated. NH: Non-Hydroalcoholic..

** Subject showing a positive response was suspected to have a pre-existing allergy to an ingredient of the product formulation.*

*** Subjects showed responses suggestive of pre-existing allergy, which were confirmed by a rechallenge with a 25% and a 10% solution of the test material. No skin reactions were observed after open application patch test for 1 hour of the test materials to these panellists. A home use test conducted with these panellits in which the test material was applied to the face and neck twice daily for 6 weeks showed no skin responses and confirmed the safety of use of the formulation in individuals with a pre-existing allergy to an ingredient of the product formulation.*

3.2.2. Subchronic and chronic toxicity

3.2.2.1. Dermal Exposure

Systemic toxicity

Animal

Pilot 14-day percutaneous subchronic toxicity studies in rabbits

Four groups of 3 male and 3 female New Zealand White rabbits each were administered topically at 2g/kg doses of one of the test articles. The test articles consisted of a vehicle solution (8% propylene glycol butyl ether in ethanol) containing 0%, 2%, 10% and 25% salicylic acid. The appropriate material was applied to the shaven intact skin of the back of each rabbit for 13 days. Following the 7 hour period of daily exposure, the application site was washed with water and gently dried. Criteria evaluated for treatment during the study period included mortality, pharmacotoxic signs, dermal irritation, body weights and gross necropsy findings. All animals survived to study termination. There were no test article related pharmacotoxic signs noted in any animal, except at the dermal site of application. Animals for all dosage groups exhibited dose-related slight to marked erythema and oedema, with the onset observed on study day 3 or 4 and continuing to day 14 in most instances. Desquamation was most often noted in the 25% salicylic acid treatment group, whereas fissuring was noted in animals from all dosage groups. These signs were generally noted on or between study days 7 to 14. Additionally, eschar was noted in the animals dosed with 10% and 25% salicylic acid and exfoliation was observed on day 13 in a 25% dosage group animal. Atonia was predominantly observed in the animals treated with 10% and 25% salicylic acid, with the onset observed on study day 8 and persisting to day 14. There were no remarkable changes in the body weights of animals noted during the study period. Moreover, at the post-mortem examination, no visible abnormalities were observed in any animal beyond the dermal irritation at the test sites (Procter & Gamble, 1993f).

A personal cleansing formulation containing 0.5% salicylic acid was applied once daily over a two week period (5 applications per week) to the intact skin of New Zealand White rabbits at concentrations of 10, 25, 50, 75 and 100%, at a dose volume of 2 ml/kg. Another group of one male and one female rabbit was treated with distilled water only and served as the control group. Duration of exposure was approximately 7 hours per day. All animals survived to termination. Mild dermal irritation in the 50, 75 and 100% groups consisted of slight erythema, fissuring and/or desquamation. No dermal irritation was observed for the 10%, 25% or the control groups. No treatment related effects were noted with respect to body weights or clinical signs (Procter & Gamble, 1990a). In a similar study, another personal cleansing formulation containing 0.5% salicylic acid (pH not indicated) caused mild dermal irritation after application at concentrations of 25, 50, 75 and 100%. The observed effects consisted of erythema, oedema, and/or fissuring and/or slight to moderate desquamation and atonia. No dermal irritation was noted in the 10% or control groups. The observed dermal effects are not likely to be due to the salicylic acid presence in the formulation since the level of salicylic acid was 0.5% in the test material and the effects were observed for some of the diluted materials in which the salicylic acid concentration was very low. As in the previous study, no treatment related effects were noted with respect to body weights or clinical signs (Procter and Gamble, 1990b).

Percutaneous subchronic toxicity studies (28-91 days) in rabbits

The subchronic percutaneous toxicity of two personal cleansing formulations containing 0.5% salicylic acid with pHs of 3.0 and 5.0 has been determined in rabbits. New Zealand White rabbits were dosed with 2 ml/kg of the test materials 5 times a week for 13 weeks. No systemic toxicity was observed in this 91-day study as evaluated by clinical signs, clinical chemistry and hematological and histopathological examinations. It was concluded that the test materials were mildly, generally transiently, irritating to the skin when applied to the intact skin of rabbit (Procter & Gamble, 1990a; 1990b).

A 28/91-day percutaneous subchronic study was conducted in male and female New Zealand White rabbits (11/sex/group) treated daily (5 times per week) with percutaneous doses of 10, 20, 40 or 120 mg/kg of salicylic acid. Salicylic acid (0.5 to 6% solutions) was applied to a shaved portion of the animals' back using a propylene glycol butyl ether/ethanol vehicle at a single dosage volume of 2 ml/kg. Also included in the study were two control groups, one in which the animals were untreated, and a second in which the animals received vehicle-treatment alone. The daily exposure period lasted approximately 7 hours after which the test articles were removed. There were no test article-related effects on survival, appearance, behavior, body weights or ophthalmoscopic examinations. Dermal applications of the tests articles resulted in slight to marked erythema, desquamation, fissuring and oedema at the site of application and slight to moderate atonia. The greatest severity for all findings was predominately noted in the 120 mg/kg group. No test article-related changes were detected in any hematological, biochemical or urological parameters. Serum salicylate concentrations increased over time up to 7 hours after dosing and decreased thereafter although they were still detected at 24 hours following dosing. A low incidence of myocardial degeneration was observed in all treatment groups and the vehicle control group. However the lesion did not reflect a dose-response relationship with respect to either lesion incidence or severity. In conclusion, the test articles would be considered dermal irritants (Procter & Gamble, 1994c, 1994d).

Human

Salicylism

Mild chronic salicylate intoxication is termed salicylism. Salicylism following percutaneous application has been well documented in the literature (Young, 1951; Cawley *et al.*, 1953; Von Weiss & Lever, 1964; Pascher, 1978; Smith & Lyons, 1980; Galea & Goel, 1989; Raschke *et al.*, 1991; Jongevos *et al.*, 1997; Chiaretti *et al.*, 1997). However, the event is rare and it is dependent among a number of factors such as the age of the patient, the degree of skin damage, the dosage level and the surface area to which it is applied (Von Weiss & Lever, 1964). The signs and symptoms of salicylic acid intoxication vary according to the susceptibility of the individual. Children are particularly susceptible to intoxication due to their small extracellular fluid volume relative to the potential surface area available for treatment as well as due to the low serum albumin concentration (Lukas, 1971; Taylor and Halprin, 1975). Age and renal function are also factors in determining susceptibility to intoxication. The plasma concentration of salicylate is increased by conditions such as renal diseases that decrease glomerular filtration rate or reduce its secretion by proximal tubules. As age increases, there seems to be a decrease in the susceptibility to salicylate toxicity. (Weigert *et al.*, 1978; Gilman *et al.*, 1990).

Plasma salicylate levels can be indicative of salicylic acid intoxication. Ordinarily, symptoms occur at plasma levels of 35 mg/100 ml or higher (Cawley *et al.*, 1953). However, a poor correlation between blood salicylate levels and the clinical severity of salicylate intoxication is sometimes found (Done, 1960). At least two factors are held responsible for this poor correlation: protein binding and blood pH. Severe salicylism has been reported in psoriatic adult patients when 6% salicylic acid was applied topically six times per day over as much as the 25% of the body surface area. Plasma levels in these patients ranged between 46 and 64 mg/100 ml over a course of 3-10 days (Von Weiss & Lever, 1964;

Brubacher & Hoffman, 1996). According to Davies *et al.* (1979), such high plasma levels were a direct consequence of the diseased state of the skin compounded by the multiple application to large areas of the body. These salicylate plasma levels are significantly higher than the plasma levels estimated for topical application of cosmetic formulations containing salicylic acid.

Conclusion

The percutaneous toxicity of salicylic acid has been evaluated in rabbits. Up to 120 mg/kg/day (the highest dose tested) applied dermally, the effect of salicylic acid was limited to dermal irritation in subchronic studies.

In humans, severe salicylism by the dermal route is rare and normally associated with diseased state of the skin compounded by the multiple application to large areas of the body. Plasma salicylate levels in these patients range between 46 and 64 mg/100 ml over a course of 3-10 days which are significantly higher than those estimated for topical administration of cosmetics containing salicylic acid.

Cumulative Skin irritation

Animal

The effects of repeated open application of 2.5% and 5% alcohol solutions of salicylic acid to the skin of guinea pigs for 3 hours, twice daily for 4 consecutive days has been evaluated (Procter & Gamble, 1982a). A summary of the results of these tests is shown in table 6. Test sites treated with the 5% alcohol solution (pH 2.32) appeared normal on days 1, 3 and 4. Barely perceptible erythema was present on 1 of 6 sites on days 2 and 5. There was no peak for skin irritation. Test sites treated with the 2.5% alcohol solution showed similar results, although there was a peak response for skin irritation on day 5 with perceptible erythema on 2 of 6 sites.

Open application of personal cleansing formulations containing 0.25% to 0.5% salicylic acid to guinea pig for 23 hours for 5 consecutive days caused minimal or no skin irritation (Procter & Gamble, 1982b).

Human

Cumulative irritation studies have been conducted to evaluate the skin irritation potential of different cosmetic product formulations containing salicylic acid, under the conditions of exposure to the product that vastly exaggerate those that would be expected amongst consumers in the market place (table 7). A total of 28 panellists completed a 3-week study, in which fully occlusive patches containing approximately 0.2 ml of 10 different test materials were applied to each subject for 24 hours, 5 times a week (Procter & Gamble, 1993q). The study was intended to compare the skin irritation potential of salicylic acid containing formulations to positive and negative irritant controls. Under the conditions of the study, formulations containing 2% salicylic acid were characterized as slightly irritating. The test allows the conclusion that, under the conditions of foreseeable use in the market place, the formulations exhibit a low potential to elicit skin irritant reactions.

Home use studies are used to obtain clinical identification and characterization of adverse effects that may be associated with repeated use of the product under conditions of use similar to those that would be expected in the marketplace (table 7). A 6-weeks, double-blind study was conducted with formulations containing 2% salicylic acid (Procter & Gamble, 1995v). Study participants received a baseline dermatological examination on week 0 and were instructed to apply their assigned product twice daily to the full face, including lower eye lids and "crow's feet" area, but to avoid application to the upper eye lids, in order to approximate conditions of product intended use in the marketplace. The products were used for 6 weeks. The subjects were instructed to record in a daily diary any adverse effects they experienced. After 6 weeks, study participants received a dermatological examination and were asked to complete a questionnaire to evaluate their reactions to the assigned product. Throughout the study there were instances of skin reactions that were considered by the study dermatologist as related to the product use and which resulted in discontinuation of the subjects from the study. None of these reactions required medical follow-up treatment. Of these 4 events, 3 users of the formulations containing 2% salicylic acid suffered a burning sensation on the face upon product application and an additional user reported the appearance of "bumps" on the face after the product use. The 6-week examination, conducted by a trained dermatological evaluator, found only sporadic instances of erythema and drynesss or scaling events. There were no instances of fissuring observed at the 6-week examination. None of the erythematous reactions were considered clinically concerning. The frequency of dryness/scaling events was even lower than for erythema and essentially comparable across all products tested (even that containing no salicylic acid).

Conclusion

The skin irritation potential of salicylic acid upon repeated application has been evaluated in guinea pigs. Product formulations or alcohol solutions containing 0.25% to 5% salicylic acid with pHs between 2.3 and 3.0 cause minimal to no irritation to guinea pig skin after repeated open application for up to 5 days.

Based on repeated-application clinical studies, formulations containing up to 2% salicylic acid have been categorized as mild transient irritants and the skin effects observed do not differ significantly from those seen with products which do not contain salicylic acid. Under the conditions of use in the market place, these products have demonstrated to have a low potential for skin irritation.

Other skin effects

Human

Salicylic acid is used in skin care formulations for its ability to promote skin exfoliation with associated improvement of the visual appearance of the skin. Although the mechanistic basis for the exfoliating activity has not been elucidated at the molecular level, this effect is generally attributed to the compound's ability to decrease corneocyte to corneocyte cohesion (Huber & Christopher, 1977; Roberts *et al.*, 1980; Goldsmith, 1979; Marchesi & Andrews, 1971). Histological examination of salicylic acid treated skin also shows an associated reduction in stratum corneum thickness in humans and in animals. Current understanding of skin function suggest that skin surface effects of this type could in theory trigger a compensatory increase in the proliferative rate of basal epidermal cells. Significantly, however, the weight of available clinical evidence indicates that topical application of salicylic acid at the levels normally found in cosmetic products, even accompanied by thinning of the stratum corneum and other surface effects, does not seem to elicit demonstrable changes in the mitotic rate of basal cells. Specifically, several investigators have reported that repeated (i.e. twice daily for 10 days) topical application of salicylic acid at concentrations up to 12% (w/v) did not enhance the proliferative rate of the basal cells measured as incorporation of ^{3}H-thymidine (Roberts *et al.*, 1980; Davies and Marks, 1976; Marks *et al.*, 1975). Given substantial gaps in the understanding of the signaling processes that mediate translation of surface events into changes in the basal cell proliferative rates, the basis for the seeming lack of effect of salicylic acid on epidermal cell proliferative rates remains unexplained. Nonetheless these observations coupled with the absence of any other data to suggest that salicylic acid may influence epidermal cell mitotic rates, constitutes a key component of the weight of evidence argument that supports the safety of the long-term use of topical formulations containing low levels of salicylic acid.

Conclusion

Repeated topical application of salicylic acid at concentrations up to 12% did not enhance the proliferative rate of basal cells measured as incorporation of ^{3}H-thymidine. Therefore, under the conditions of consumer exposure anticipated for topical products containing 2% salicylic acid, there appears to be minimal risk of eliciting clinically significant alterations in epidermal homeostasis.

Table 6: Non-clinical skin irritation studies

Test type	Test material	Test conditions	Results	Reference
ROAT				
Guinea pig irritation	• 2.5% SA in alcohol solution, pH 2.34 • 5% SA in alcohol solution, pH 2.32	0.15 ml open application for 3 hours, twice a day for 4 consecutive days	Mildly irritating	P&G, 1982a
Guinea pig irritation	• HC[1]/0.5% SA, pH 2.90 • HC[1]/0.25% SA, pH 2.7-3.0	0.25 ml open application for 23 hours, once daily for 5 consecutive days	Minimal skin irritation	P&G, 1982b
Guinea pig irritation	• HC[1]/0.5% SA, pH 2.70	0.25 ml open application for 23 hours, once daily for 5 consecutive days	Non-irritating	P&G, 1983

ROAT: Repeated Open Application Test. SA: Salicylic acid. ASA: Acetylsalicylic acid.[1] HC: Hydroalcoholic cleanser.

Table 7: Clinical studies to address skin effects

Study type	SA (%)	pH	Test conditions	Results	Reference
Cumulative irritation*					
21-day NH cream	1.5	NI	Occlusive patch, undiluted product, 5x/week, 21 days.	0/27 Adverse reactions Test substance: slightly irritating vs. control.	P&G, 1993q
21-day Hydroalcoholic gel	2%	NI	Semi-occlusive, undiluted product, 5x/week	0/28 Adverse reactions Test substance: slightly irritating vs. control.	P&G, 1993r
21-day NH cream	2	NI	Occlusive patch, undiluted product, 5x/week, 21 days. Panellists with self-assessed sensitive skin included (50% of total panellists)	0/25 Adverse reactions Test substance: Moderately irritating vs. control.	P&G, 1993w
21-day NH cream	2	NI	Occlusive patch, undiluted product, 5x/week, 21 days. Panellists with self-assessed sensitive skin included (50% of total panellists)	0/25 Adverse reactions Test substance: Non irritating vs. control.	P&G, 1993v
5-day NH cream	2	NI	Occlusive and Semi-occlusive patches, 1, 5 and 15% solutions, 5 days	0/28 Adverse reactions Test substance (15%): Non irritating	P&G, 1995r
14-day Surfactant-based product	2	3.8	Occlusive patch, 4% aqueous solution, 24h, 6x/week, 14 days.	Product found to be cumulative irritant but classified as 'probably mild under normal use conditions	J&J, 3
12-day Surfactant-based product	NI	NI	Occlusive patch, 24h, 7x/week, 12 days.	6/25 Minimal erythema, 2/25 definite erythema, 9/25 erythema and papule, 1/25 definite edema. Substance classified as probably mild in normal use conditions.	J&J, 1
12-day Surfactant-based product	2	3.8	Occlusive patch, 1% aqueous solution, 24h, 7x/week, 12 days.	0/26 Adverse reactions. Substance classified as mild - no experimental irritation.	J&J, 2
Back irritation					
14-day back irritation study NH moisturizer and hydroalcoholic lotion	2	NI	ROAT, undiluted product, 2x/day, 5x/week, 1x/weekend, 14 days	Moisturizer produced significantly higher hydration than no treatment control. No differences between test article and control in irritation and skin dryness	P&G, 1995s

SA: Salicylic acid. NI: Not indicated.. SLS: Sodium Lauryl Sulfate. ROAT: Repeated Open Application Test. NH: Non-Hydroalcoholic

** Positive (0.2-0.25% SLS) and negative (water) controls were included in all P&G Cumulative irritation studies.*

Table 7: Clinical studies to address skin effects (cont.)

Study type	SA (%)	pH	Test conditions	Results	Reference
Facial appearance /irritation					
14-weeks NH lotions and moisturizers with/without salicylic acid	2	2.28	Home use test	12/194 Adverse effects consisting on itching and stinging, redness, mild erythema, burning feeling, irritated upper eye-lid and skin reaction on finger. Substance responsible for adverse reactions not identified.	P&G, 1994/95h
6-week NH lotion	2	NI	Home Use test	Dermatologic findings were generally mild, transient and/or sporadic in all products tested (even those with no salicylic acid).	P&G, 1995v
12-weeks NH cream, hydroalcoholic gel and lotion	NI	NI	Neat product applied 2x/day, 5x/week	Cream showed improvement in irritation and dryness versus lotion	P&G, 1993s
6-week NH cream	2	NI	Home Use test	57 panellists of which 30 had self-assessed sensitive skin. No adverse reactions observed. Profile of skin responses consistent with the use of products with little or no irritation potential.	P&G, 1993z
2-weeks Hydroalcoholic lotion	0.5	2.82	Forehead and nose daily application	0/14 Adverse effects observed. No evidence of skin irritation	P&G, 1993t

SA: Salicylic acid. NI: Not indicated. +ve: positive. -ve: negative. SLS: Sodium Lauryl Sulfate. ROAT: Repeated Open Application Test. NH: Non-Hydroalcoholic

3.2.2.2. Oral Exposure

Systemic toxicity

To date there are no published non-clinical studies which examine oral toxicity of salicylic acid. There is, however, information on acetylsalicylic acid-related toxicity following oral administration. Given the metabolic profile of orally absorbed acetylsalicylic acid and its rapid hydrolysis to salicylic acid, the available animal data concerning acetylsalicylic acid has been judged to have some relevance to salicylic acid. However, it should be considered that clinically salicylic acid is often considered ineffective when compared to acetylsalicylic acid. For example, laboratory studies have demonstrated that non-acetylated salicylates are at least 10 (in vitro) to 60-fold (in vivo) less effective in increasing bleeding times than acetylsalicylic acid (O'Brien, 1968; Mills et al., 1974).

Animal

An oral dosing study with acetylsalicylic acid in which rats were treated orally with 200 mg/kg/day for 200 days has been conducted (Thomas *et al.*, 1977). The treatment did not produce any signs of toxicity or deaths. Acetylsalicylic acid did not alter urinary lactic dehydrogenase or alkaline phosphatase activity. Histopathological examination of the animals' heart, lung and kidney tissues failed to detect any significant changes when compared to the controls.

Human

Ingestion of acetylsalicylic acid tablets is the most frequent cause of salicylate poisoning. In neonates, infants and children other less common causes include application of teething gels to gums (Paynter & Alexander, 1979), placental transfer (Ahlfors et al., 1982; Lynd et al., 1976) and breast milk (Clark & Wilson, 1981).

Plasma salicylate levels can be indicative of salicylic acid intoxication. Ordinarily, symptoms occur at plasma levels of 35 mg/100 ml or higher (Cawley *et al.*, 1953). However, a poor correlation between blood salicylate levels and the clinical severity of salicylate intoxication is sometimes found (Done, 1960). At least two factors are held responsible for this poor correlation: protein binding and blood pH. When salicylate intoxication is reviewed on a mg/kg basis, little or no toxicity is seen in adults ingesting less than 150 mg/kg.

Chronic salicylate toxicity can result from long-term exposure to salicylate at doses of 100 mg/kg or greater. It is manifested principally as tinnitus, hearing loss, dimness of vision, headache, dizziness, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, increased heart rate, nausea, vomiting and occasionally diarrhea. However, if intoxication is severe, other manifestations associated with acute intoxication may occur. Acute salicylate overdose has symptoms similar to those of chronic intoxication, but the effects are often more pronounced or occur in more rapid succession. The principal physiologic manifestations of acute salicylism are acid-base disturbances, dehydration, fever and hyperglycemia or hypoglycemia.

Conclusion

Chronic salicylate toxicity can result from long-term exposure to salicylates by the oral route. In animal studies, a NOEL of 200 mg/kg/day has been established for acetyl-salicylate.

In humans, oral doses of acetylsalicylic acid of 100 mg/kg or greater are needed for toxicity (salicylism) to occur. Plasma levels of salicylates of 35 mg/100 ml or higher are required for toxicity to occur. These plasma salicylate levels are significantly higher than those estimated for topical administration of cosmetics containing salicylic acid.

3.2.3. Reproductive toxicity

Animal

To date there are no published studies which examine reproductive, fetotoxic or teratogenic effects following **topical** application of salicylic acid. There is, however, information on acetylsalicylate-related reproductive toxicity following **oral** administration. Given the metabolic profile of orally absorbed acetylsalicylatic acid and its rapid hydrolysis to salicylic acid, the available animal data concerning acetylsalicylic acid has been judged to have some relevance to salicylic acid. Because of the earlier-mentioned differences in metabolism and pharmacology, it should, however, be considered that clinically salicylic acid is often considered ineffective when compared to acetylsalicylic acid. For example, laboratory studies have demonstrated that non-acetylated salicylates are at least 10 (*in vitro*) to 60-fold (*in vivo*) less effective in increasing bleeding times than acetylsalicylic acid (O'Brien, 1968; Mills *et al.*, 1974).

Evidence from animal studies suggest that acetylsalicylic acid ingestion during the latter portion of gestation can have adverse effects on both the mother and the fetus. The administration of 200 mg/kg/day of acetylsalicylic acid to rats during the last 6 days of pregnancy resulted in a prolongation of labor and parturition time, which was attributed to impaired prostaglandin synthesis, and increased incidences of in-utero fetal death (Tuchman-Duplessis *et al.*, 1975).

Mated Charles River Crl:CD® VAF/Plus® female rats, consecutively assigned to one control and three treatment groups and one positive control group were used in a toxicity study to determine the possible adverse effects of the test article, sodium salicylate, on parturition and neonatal viability. Twenty five females each were assigned to the vehicle control, the low and the mid dose, whereas 16 females were assigned to the high dose and the positive control group. Dosage levels of 20, 80 and 200 mg/kg/day were administered orally by gavage twice daily on gestation days 15 through 21 at a volume of 20 ml/kg. The positive control group received acetylsalicylic acid at a total daily dosage of 261 mg/kg on the same regimen as the test article-treatment group. The control group received the vehicle only, 0.5% low viscosity carboxymethylcellulose, on a comparable regime. All dams were allowed to deliver. Surviving dams and pups were euthanized on lactation day 1. Administration of 200 mg/kg/day salicylic acid and of 261 mg/kg/day acetylsalicylic acid induced maternal toxicity (agonal clinical signs and/or inhibition of body weights and food consumption) late in gestation and early in lactation. This was generally linked to prolonged parturition and difficulty in delivery, and there was a corresponding adverse effect on offspring survival for the affected dams. Additional developmental toxicity, in terms of reduced offspring body weight at birth, was noted in these groups but did not appear to be closely linked to specific dams with severe toxicity. With the exception of a slight, but not statistically significant increase in mean parturition length, due primarily to one female with a parturition length of 12 hours, there was no evidence of adverse effects on the adults or the offspring in the mid-dose (80 mg/kg/day) group. There was no test article-related maternal toxicity, developmental toxicity or evidence of adverse effects on the process of parturition in the low-dose (20 mg/kg/day) group. In conclusion, the NOAEL of sodium salicylate when administered orally to mated rats was 80 mg/kg/day with regard to maternal toxicity and developmental toxicity (Procter & Gamble, 1994e).

Human

Although reproductive toxicity effects have been observed in rodents after administration of acetylsalicylic acid, there is no solid evidence to link ingestion of normal therapeutic doses to reproductive effects in humans.

In six independent clinical trials in which low-dose acetylsalicylic acid (60-150 mg/day) was administered during the second and third trimesters of pregnancy for the treatment of preeclampsia, there was no evidence of acetylsalicylic acid-related adverse effects on the mother or on the newborn (Dekker & Sibai, 1993). Moreover, a multicentered, randomized, placebo-controlled double-blind trial including 471 women with insulin dependent diabetes, 774 with chronic hypertension, 688 with multifetal gestation and 606 with preeclampsia in a previous pregnancy, treated daily between weeks 15-26 of gestation, found that acetylsalicylic acid (60 mg) did not increase maternal or perinatal bleeding complications (Caritis, 1997).

In humans, only in cases of daily ingestion of high levels of acetylsalicylic acid (3200 mg/day) by mothers with muscoskeletal disease has been associated with extended labor and parturition time, and increased incidence of delivery complications and postpartum hemorrhage (Lewis & Schulman, 1973; Collins & Turner, 1975). Perinatal mortality and low birth weight have also been associated with acetylsalicylic acid exposure in retrospective clinical studies (Turner & Collins, 1975; Nelson & Forfar, 1971), however, because of the restrospective design of these studies and/or the inclusion of mothers with rheumatic disorders, the interpretation of these results is difficult. Importantly, these observations found no support in a considerably larger prospective study which included more than 14,000 mothers (Shapiro *et al.*, 1976).

Salicylate-related maternal reproductive effects are believed to be the result of decreased prostaglandin synthesis (Lewis & Schulman, 1973). Both acetylated and non-acetylated salicylate have shown to diminish prostaglandin levels in human clinical studies and *in vitro* models, but the mechanism for inhibition of prostaglandin synthesis appears to differ between acetylated and non-acetylated salicylate (Moncada & Vane, 1979).

Both, non-acetylated salicylate and acetylsalicylic acid interact with a supplementary binding site on the cyclo-oxygenase enzyme which is critical to the synthesis of prostaglandins from arachidonic acid, but the interaction of non-acetylated salicylate is transitory. Acetylsalicylic acid acetylates a serine residue and thus irreversibly inhibits the enzyme activity (Roth & Siok, 1978). Non-acetylated salicylates, such as salicylic acid, bind reversibly to cyclo-oxygenase and thus their clinical effects will only occur and persist as long as there is an effective systemic concentration (Miller & Prichard, 1990).

Salicylates readily cross the placental barrier (Levy & Garrettson, 1974; Palmisano & Cassady, 1969). Systemic elimination of salicylate is also slower in the fetus (Levy & Garrettson, 1974; Palmisano & Cassady, 1969). Consequently, the plasma salicylate levels in the fetus are likely to be larger than those of the mother. It has also been suggested that the neonates are more sensitive to the effects of acetylsalicylic acid on platelet aggregation.

The mechanisms of salicylate-related neonatal hemorrhaging has not been determined, but both platelet dysfunction and decreased clotting factor XII have been reported in acetylsalicylic acid-exposed neonates (Corby & Schulman, 1971; Bleyer & Breckenridge, 1970). Importantly, non-acetylated salicylates, such as salicylic acid, have only limited and transitory clinical effects on platelet function and thus have been proposed as the preferred compounds for treatment if therapy is needed prior to surgery or in patients at risk for bleeding (Miller & Prichard, 1990).

Conclusion

In rats, the NOAEL for sodium salicylate when administered orally to mated rats has been found to be 80 mg/kg/day with regard to maternal toxicity and developmental toxicity.

However, there is no evidence to link ingestion of normal therapeutic doses to reproductive effects in humans. Reproductive effects have not been observed in humans when low therapeutic doses of acetylsalicylic acid (60-150 mg/day) have been administered to women during pregnancy. Clinical incidence of acetylsalicylic acid-related increases in labor gestation times and postpartum hemorrhaging have only been noted at doses of 3200 mg/day in patients with musculoskeletal disorders. Furthermore, there is an extensive body of evidence that documents that salicylic acid is often considered ineffective clinically when compared to acetylsalicylic acid. Regarding bleeding times, literature data indicates that salicylic acid is at least 10 (*in vitro*) to 60 (*in vivo*) times less potent than acetylsalicylic acid, which could be the result of the limited and transitory clinical effects on platelet function typical of non-acetylated salicylates.

Table 8: Clinical maternal reproductive toxicity/fetotoxicity studies

Study	Test article	Test conditions	Results	Reference
Prospective	Acetyl salicylate	10 women ingesting acetylsalicylic acid within 1 week prior of delivery	• 8/10 women showed impaired platelet function • All 10 infants showed platelet dysfunction	Corby & Schulman, 1971
Prospective	Acetyl salicylate	41,337 pregant mothers and offspring in 3 groups: not exposed (14,956), intermediate (24,866) and high (1515)	• No significant differences between the group death rates and the average birth weights	Shapiro *et al.*, 1976
Prospective	Acetyl salicylate	6 independent clinical trials with a total of 370 pregnant women ingesting acetylsalicylic acid (60-150 mg) daily during 2nd and 3rd trimesters versus 285 women receiving placebo for treatment of preeclampsia	• Blood loss equal in both groups. • No excess bleeding observed • No premature closure of ductus arteriosus observed in newborns • low dose acetylsalicylic acid showed to be effective in prevention of preeclampsia and fetal growth retardation	Dekker & Sibai, 1993
Prospective	Acetyl salicylate	2,539 women ingesting acetylsalicylic acid (60 mg) or placebo daily from 3rd month of pregnancy until delivery	• Acetylsalicylic acid did not increase maternal or perinatal bleeding complications	Caritis *et al.*, 1997
Retrospective	Acetyl salicylate	272 consecutively delivered infants	• 26 had detectable levels of salicylate in umbilical cord serum (average concentration: 3.3 mg/100 ml) • Mean albumin binding capacity significantly depressed, but serum protein levels unchanged.	Palmisano & Cassady, 1969
Retrospective	Acetyl salicylate	14 newborn exposed during the week prior to birth, 17 infants not-exposed	• Exposed infants showed platelet dysfunction and decreased factor XII activity	Bleyer & Breckenridge, 1970
Retrospective	Acetyl salicylate and other analgesics	Mothers who consumed drugs during pregnancy and had infants with congenital deformities and those without	• Significant increase in malformation rate for infants whose mothers took analgesics during the first 28 days of pregnancy • Congenital malformations included hydrocephalus, congenital heart disease, mongolism and dislocation of the hip.	Nelson & Forfar, 1971
Retrospective	Acetyl salicylate	103 rheumatoid patients consuming 3250 mg/day for 6 months	• Average gestation period 1 week longer than healthy and non-treated control groups • Longer labor times (12.1 hours) than control groups (5-7.3 hours) • Greater blood loss than controls	Lewis & Schulman, 1973
Retrospective	Acetyl salicylate	144 women in 3 groups: High: 63 mothers, daily consumption Intermediate: 81 mothers, weekly consumption Control: 63 mothers, no consumption	• Gestation and postpartum hemorrhage significantly increased in high and intermediate groups • Still birth and perinatal death rate increased in high and intermediate groups • Decreased birth weight for high and intermediate groups • Study does not support teratogenic activity but suggests that chronic ingestion may be associated with an increase in perinatal mortality and decreased intrauterine growth.	Collins & Turner, 1975
Retrospective	Analgesics	144 mothers in 3 groups: High: daily consumption Intermediate: weekly consumption Control: no consumption	• Lower birth weights in infants of high group versus other two groups • Blood level of salicylate for high group ranged between 0 and 7 mg/100 ml and neonates born to these women had salicylate levels of 0-14 mg/100 ml	Turner & Collins, 1975

It should be noted that the results of the retrospective studies are difficult to interpret based on the limitations typical of such studies and the fact that most of these studies included mothers with rheumatic disorders and/or mothers ingesting acetylsalicylic acid in combination with other drugs or were conducted without appropriate control groups. Prospective studies conducted with appropriate control groups under defined conditions are normally considered necessary to confirm or invalidate the conclusions of a retrospective study. Prospective studies conducted with pregnant women exposed to low therapeutic doses of acetylsalicylic acid did not confirm the results of the retrospective studies. Prospective studies have shown no evidence of reproductive toxicity due to the administration low therapeutic doses of acetylsalicylic acid.

3.2.4. Teratogenicity

Animal

The fetotoxic and teratogenic potential of salicylate in rodents has been evaluated. Numerous studies with acetylsalicylic acid and some with salicylic acid at daily doses of 75 to 500 mg/kg in rats, mice and hamsters administered at various times during pregnancy have demonstrated increased rates of fetal malformations, resorptions and perinatal death (Warkany and Takacs, 1959; Wilson *et al.*, 1971; Wilson, 1977; Erickson and Larsson, 1966; Trasler, 1965; Tanaka *et al.*, 1972, 1973; Kimmel *et al.*, 1971; Wilson, 1971). These studies are summarized in table 9.

Mechanistic studies have determined that salicylic acid is the causative agent for salicylate-related adverse fetal effects (Kimmel *et al.*, 1974). In studies with the most sensitive animal model (rat) for salicylic acid-related teratogenicity, Tanaka *et al.* (1973) noted only a low incidence of skeletal malformations (3/26 fetuses examined had extra ribs, compared with 2/29 in controls) and external malformations (1.8%) in offspring females treated with salicylic acid at a dose of 75 mg/kg/day during days 7 to 17 of gestation. The LOEL for teratogenicity was estimated as 75 mg/kg/day.

Studies with non-human primates have shown them to be less susceptible than rats to salicylate-induced fetotoxicity and teratogenicity (Wilson *et al.*, 1977; Wilson, 1971). Comparative studies between rats and monkeys have demonstrated significant differences in the volume of distribution and pharmacokinetics for salicylate following oral dosing (Wilson *et al.*, 1977). The total plasma concentrations of salicylic acid were generally higher in rats than in monkeys at comparable doses. Importantly, it was also noted that a higher percentage of the total concentration of salicylic acid remains unbound in the rat than in the monkey. Thus, the rat embryo is exposed to greater levels of salicylic acid for twice as long as is the monkey embryo when each species was given an equivalent oral dose. These findings provide an explanation for the sensitivity of the rodent model as compared to the non-human primate for salicylic acid-induced teratogenicity. The NOEL in the non-human primate model for salicylate-related teratogenic effects is 100 mg/kg/day.

Human

Studies on the teratogenic activity of salicylates in humans have been summarized in table 10. A large prospective clinical study of 14,000 mothers and their infants found that the use of oral salicylate during pregnancy was not associated with congenital malformations (Slone *et al.*, 1976). Although in some retrospective studies and a case study involving mothers with rheumatic disorders, a variety of congenital malformations have been associated to acetylsalicylic acid exposure during gestation (McNeil, 1973; Richards, 1969; Turner & Collins, 1975; Zierler & Rothman, 1985), these results have not been confirmed by more recent prospective studies conducted with more than 10,000 pregnant women exposed to 60-80 mg/day acetylsalicylic acid during the second and third trimester of gestation (Herz-Picciotto *et al.*, 1990; Di Sessa et al., 1994). First trimester use of acetylsalicylic acid was addressed in a large prospective study including more than 50,000 mother-child pairs (Herz-Picciotto *et al*, 1990). The results from this study did not show an increased risk of congenital malformations as a consequence of the ingestion of acetylsalicylic acid during the first trimester of pregnancy. Werler *et al.* (1989) also found that acetylsalicylic acid use at normal therapeutic doses during the first trimester of pregnancy does not increase the risk of congenital heart defects. These results have been confirmed by Shaw *et al.* (1990) and Tikkanen & Heinonen (1992).

Exposure to salicylates late in gestation has also been associated with pre-term closure of the ductus arteriosus in animal and human studies. The changing role of the ductus arteriosus is mediated by prostaglandins. At birth, cyclo-oxygenase inhibitors normally constrict the ductus. In animals a single dose of acetylsalicylic acid during the later part of the gestation has been associated with constriction of the ductus arteriosus through the inhibition of prostaglandin synthesis (Momma & Takeuchi, 1983; Heymann & Rudolph, 1976). However, doppler investigation of fetuses aged 15-40 weeks exposed to 60 mg acetylsalicylic acid daily during the second and third trimester did not reveal any effect on the ductus arteriosus (Di Sessa et al., 1994). It has been postulated that low dose acetylsalicylic acid

inhibits selectively thromboxane, but does not impair prostacyclin production (Kaaja *et al.*, 1993). Therefore, it is likely that high doses of acetylsalicylic acid will be required for the appearance of ductus arteriosus as a consequence of the inhibition of prostaglandin synthesis. Given the reversibility of the inhibition of prostaglandin synthesis by non-acetylated salicylates (Miller & Prichard, 1990), even higher and continuous doses would be required for salicylic acid to lead to such effect.

Conclusion

In rats, a LOEL of 75 mg/kg/day has been reported. However, the NOEL in the non-human primate model for salicylate-related teratogenic effects is 100 mg/kg/day, given their lower susceptibility to salicylate-induced fetotoxicity and teratogenicity.

Although high doses of salicylates are teratogenic in rodent models, there is no solid evidence to link ingestion of usual therapeutic doses of salicylate to teratogenic events in humans. At normal therapeutic levels (60-150 mg/day), large prospective studies have found no evidence that acetylsalicylic acid consumption during pregnancy leads to congenital malformations or the appearance of ductus arteriosus.

Table 9: Teratogenicity studies with acetylsalicylic acid or salicylic acid

Species	Test article	Route of exposure	Dosage	Results	Reference
Rats	Methyl salicylate	Injection Days 9, 10 and 11 of gestation	0.1 to 0.5 ml	• 47/116 animals reabsorbed their young. • 45/298 offspring showed abnormalities including cleft lip, eye defects and hydrocephaly • 75/298 offspring had skeletal deformities	Warkanay & Takacas, 1959
Mice (C57BL/6 and A/JAX)	Acetyl salicylate	Oral Days 8 and 9, or 9 and 10 of gestation	500 mg/kg/day	• Significant increase incidence of cleft lip • Increase in malformations, including short snout, exencepahly, polydactyly and spina bifida • Effect level: 500 mg/kg/day	Trasler, 1965
Rats	Acetyl salicylate	Oral Days 9 to 11 of gestation	250-1000 mg/kg/day	• Malformations (hydrocephaly, clubfoot, skeletal dysplasia and extra ribs) in a dose dependent manner • Teratogenic effect attributed to increased maternal serum concentrations of salicylic acid • Effect level: 250 mg/kg/day	Kimmel *et al.*, 1974
Rats	Acetyl salicylate or salicylate	Oral Days 8 to 14 of gestation	75, 150 and 300 mg/kg/day	• 300 mg/kg/day animals died shortly after dosing • Significant increase incidence of abnormalities for both test articles at 150 mg/kg/day • Extremely low incidence of anomalies at 75 mg/kg/day • LOEL: 75 mg/kg/day	Tanaka *et al.*, 1973
Rats	Salicylate	Oral Days 8 to 14 of gestation	0.06% to 0.4% in diet	• Temporary body weight loss and toxic symptoms at the 0.4% group with a high rate of mortality and growth retardation in fetuses • Doses of 0.1% or lower did not cause any significant effects	Tanaka *et al.*, 1973
Rats	Acetyl salicylate	Oral Days 9 to 12 of gestation	100 and 150 mg/kg/day	• Rats: 100 mg/kg./day did not cause fetotoxicity, but 150 mg/kg/day caused death and reabsorption in 34% of the embryos	Wilson *et al.*, 1977
Monkeys	Acetyl salicylate	Oral Days 23-32 of gestation	100 and 150 mg/kg/day	• Monkeys: Both dosages caused transient growth retardation. Doses of 150 mg/kg/day caused malformations in 3/15 fetal monkeys at 32-days of gestation and 1 / 4 in 100-day fetal monkeys. No malformations observed at 100 mg/kg/day.	Wilson *et al.*, 1977
Rats	Acetyl salicylate	Oral Days 7 to 17 of gestation	50, 100 and 200 mg/kg/day	• Decrease in maternal body weight gain in all groups • Significant increase in resorption and fetal malformations in the 200 mg/kg/day group • Decreased fetal body weights observed for 100 and 200 mg/kg/day groups.	Nakatsuka & Fujii, 1979

Table 10: Teratogenicity studies in humans

Study	Test article	Test conditions	Results	Reference
Prospective	Acetyl salicylate	50,282 women exposed during the first 4 months of pregnancy and offspring	• Malformations similar in infants of women not exposed (30,418), intermediate exposed (9736) and heavily exposed (5128)	Slone *et al.*, 1976
Prospective	Acetyl salicylate	Pregnant women ingesting 60 mg/day acetylsalicylic acid or placebo	• No adverse effect observed on circulation of fetuses or newborns	Di Sessa *et al.*, 1994
Retrospective	Salicylates	833 infants who demonstrated congenital malformations and matched controls	• Significant increases in malformation rates for mothers ingesting salicylates in the first trimester • Malformations noted in central nervous system and alimentary tract • Mongolism and effects on eye, ear, urogenital and skin observed	Richards, 1969
Case studies	Salicylates	8 infants born to mothers ingesting salicylates during early pregnancy, in most cases in combination with other drugs	• Authors suggest salicylate may cause teratogenic events if ingested in first 60 days of pregnancy • Clinical malformations in infants were shortened forearm, defect in digit number and size, cleft palate and congenital heart defects	McNeil, 1973
Retrospective	Acetyl salicylate	Infants with structural cardiac defects (1381) versus infants with other malformations (6966) with mothers who ingested or not acetylsalicylic acid during first trimester of pregnancy.	• No dose effect pattern was identified for cardiac effects • Use of acetylsalicylic acid during the first trimester of pregnancy does not increase the risk of congenital cardiac defects in relation to other malformations	Werler *et al.*, 1989
Retrospective	Acetyl salicylate and other drugs	Pregnant mothers ingesting acetylsalicylic acid and other drugs during pregnancy	• No association observed for maternal use of acetylsalicylic acid and congenital malformations in the new born	Shaw *et al.*, 1990
Retrospective	Salicylates	406 women with congenital heart disease in the offspring	• No association found between maternal use of contraceptive pills, salicylates, diazepam or sweetening agents and the risk of congenital heart disease in the resulting offspring	Tikkanen & Heinonen, 1992

3.2.5. Genotoxicity and carcinogenicity

Animal

Results from Ames tests using concentrations of salicylic acid and acetylsalicylic acid as high as 500 µg/ml, with or without metabolic activation, have been uniformly negative in several bacterial strains (McCann *et al.*, 1975; Kawachi *et al.*, 1979). No significant increase in the number of histidine independent revertants was demonstrated following exposure to salicylic acid at concentrations of 3 to 8 x 10^{-5} M (Zetterberg, 1979). However salicylic acid and acetylsalicylic acid have been reported to be mutagenic in *Bacillus subtilis* (rec assay) using non-activated conditions (Kawachi *et al.*, 1979). Salicylic acid (1.5-25 mg/ml) was demonstrated not to be clastogenic in cultured CHO cells both with and without metabolic activation (Stich *et al.*, 1981), and in contrast, reported to be clastogenic when Chinese hamster lung cells were treated, under non-activating conditions, with 1.00 and 1.25 mg/ml salicylic acid (Ishdate, 1988). The reason for the apparent discrepancy between these two studies is likely due to different treatment conditions, 3 hour exposure in the first study versus 48 hours in the latter. Finally, *in vivo* treatment of *D. melanogaster* with 10mM acetylsalicylic acid did not cause increased mutagenic or lethal effects in the drosophila sex-linked recessive lethal assay (King *et al.*, 1979). Thus results from mutation tests for both salicylic acid and acetylsalicylic acid generally have been negative under the relevant conditions of metabolic activation.

Beyond the *in vitro* tests, there is one report that acetylsalicylic acid has been tested in a carcinogenicity bioassay at dosages, in drinking water, of 1 and 5% in mice and 0.25 and 2% in rats. Results from these studies were uniformly negative and support that acetylsalicylic acid is not carcinogenic. Since acetylsalicylic acid is metabolized to salicylic acid, the data from the acetylsalicylic acid bioassay provides strong support that salicylic acid is not carcinogenic (Odashima, 1979). Salicylic acid was tested as part of a skin tumor promotion study using uninitiated mouse skin (Boutwell & Bosch, 1959). A 20% salicylic acid in dioxane solution was applied topically to mice twice weekly for 12 weeks. There were no deaths or papillomas throughout the study, however there was no post-mortem examination conducted at the end of the treatment period and so these results provide limited value for the toxicological perspective on this ingredient. Recent epidemiological evidence has shown that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer (Thun *et al.*, 1991). This activity of acetylsalicylic acid has been associated with the inhibiting action of acetylsalicylic acid on sulphotransferases. Salicylic acid has also been shown to interact with phenolsulphotransferase and therefore it has been proposed that this could be one of the pathways by which acetylsalicylic acid reduces cancer risk (Harris *et al.*, 1998)

Conclusion

There are conflicting reports for the *in vitro* genotoxic potential of salicylic acid and acetylsalicylic acid. However, carcinogen bioassay data for acetylsalicylic acid were negative and provides compelling overriding support that salicylic acid is not a carcinogen.

3.2.6. Drug interactions

Human

Salicylates interact with a number of drugs when administered orally at therapeutic doses. In addition, the repeated daily topical application of 6% salicylic acid gels on a prescription basis to areas of extremely compromised skin could theoretically result in potential drug interactions. Therapeutic topical application of 6% or higher salicylic acid preparations under conditions of large surface area involvement or occlusion has lead to significant serum salicylate levels in individuals with compromised skin.

Under these conditions or situations of medium to high oral dosing, salicylate interactions with drugs such as hypoglycaemics and methotrexate may occur (Hecht, 1981; Alvan *et al.*, 1981). These drugs, as do salicylate, bind non-specifically with serum proteins. Drug interactions are theoretically possible due to competition of salicylate with other drugs for binding the serum albumin. This would ultimately result in the potentiation of hypoglycemia in individuals using hypoglycemics, such as tolbutamide, or clinical toxicity related to methotrexate in individuals using this latter drug at large doses (Baker, 1970). Acetylsalicylic acid is bound to a more limited extent to plasma proteins than salicylic acid, however it acetylates the human plasma albumin and changes the binding affinity of drugs to serum albumin. Salicylic acid lacks a reactive acetyl moiety and thus would not contribute to decreased available plasma binding sites by this mechanism.

Potential drug interactions may also occur with anticoagulants, uricosuric agents as well as with other non-steroidal anti-inflammatory agents (Yu *et al.*, 1990; Miners, 1989). Salicylate may enhance the anticoagulant activity of drugs such as warfarin and increase the risk of bleeding complications by several mechanisms. It appears that high doses of acetylsalicylic acid (greater than 3 g/day) are required to enhance activity of oral anticoagulants. The activity of uricosuric agents, such as phenylbutazone, probenecid or sulfinpyrazone, are antagonistic. The exact mechanism of their interaction has not been established. However, studies with probenecid-induced uricosuria demonstrate that serum salicylate levels much higher than those achieved by topical application of cosmetics are necessary to produce clinically important interactions. Salicylate appears to have various interactions with other non-steroidal antiinflammatory agents, however most of the interactions that have been studied have little clinical importance. Concurrent administration of acetylsalicylic acid with other non-steroidal anti-inflammatory agents appears to alter the absorption, excretion and metabolism of some agents. Acetylsalicylic acid also potentiates the ulcerogenic effects of caffeine, indomethacin and phenyl butazone (Gilman *et al.*, 1990).

Conclusion

The plasma levels resultant from the exposure to cosmetic formulations containing salicylic acid are not likely to saturate all available binding sites, because consideration must be given to the time-dependent absorption of salicylic acid through the skin plus the relatively short half-life of salicylic acid under low dose conditions. The metabolic capacity for salicylic acid clearance in the body is not saturated until serum salicylate levels exceed 150-300 µg/ml. Therefore, clinical drug interaction from the topical use of cosmetic products is improbable.

LITERATURE REFERENCES

1) Ahlfors C.E., Schwer M.L. and Ford K.B. Bilirubin-albumin binding in neonatal salicylate intoxication. *Develop. Pharmacol. Ther.*, 1982, **4**: 47-60.

2) Alvan G., Bergman U and Gustafsson L.L. High unbound fraction of salicylate in plasma during intoxication. *Br. J. Clin. Pharmacol.*, 1981, **11**: 625-626.

3) Arita T., Hori T., Washitake M., Akatsu M. and Yajima T. Studies on the percutaneous absorption of drugs. *Chem. Pharm. Bull.*, 1970, **18**: 1045-1049.

4) Baker . Intermittent high dose oral methothrexate theray in psoriasis. *Br. J. Dermatol.*, 1970, **82**: 65-69.

5) Bart B.J., Biglow J., Corwin V.J. Salicylic acid in Karaya gum patches as a treatment for verruga vulgaris. *J. Am. Acad. Dermatol.*, 1989, **20**: 74-76.

6) BIOFAX 21-3/1971. BIOFAX Industrial Bio-test Laboratories, Inc., Data Sheets. 1810 Frontage Rd., Northbrook, IL 60062.

7) Birmingham B.K., Greene D.S. and Rhodes C.T. Percutaneous absorption of salicylic acid in rabbits. *Drug. Dev. Indust. Pharm.*, 1979, **5**: 29-40.

8) Bleyer W.A. and Breckenridge R. Studies on the detection of adverse drug reactions in the newborn. II. The effects of prenatal aspirin on newborn hemostasis. *J. Am. Med. Assoc*, 1970, **213**: 2049-2053.

9) Boutwell R.K. and Bosch D.K. The tumor-producing action of phenol and related compounds for mouse skin. *Cancer Res.*, 1959, **19**: 413-427.

10) Brubacher J.R. and Hoffman R.S. Salicylism from topical salicylates: review of the literature. *J. Toxicol. Clin. Toxicol.*, 1996, **34**: 431-436.

11) Bunney M.H., Nolan W.M. and Williams D.A. An assessment of methods of treating viral warts by comparative treatment trials based on standard design. *Br. J. Dermatol.*, 1976, 94: 667-679.

12) Caritis S.N. Low dose aspirin does not prevent preeclampsia in high risk women. *Am. J. Obstet. Gynecol.*, 1997, **176**: S3.

13) Cassano N., Alessandrini G., Mastrolonardo M. and Vena G.A. Peeling agents: toxicological and allergological aspects. *J. Eur. Acad. Dermatol. Veneorol.*, 1999, **13**: 14-23.

14) Cawley E.P., Peterson N.T. and Wheeler C.E. Salicylic acid poisoning in dermatological therapy. *JAMA*, 1953, **151**: 372-374.

15) Chiaretti A., Schembri-Wismayer D. Tortorolo L., Piastra M. and Polidori G. Salicylate intoxication using a skin ointment. *Acta Pediatr.*, 1997, **86**: 330-331.

16) Clarke J.H. and Wilson W.G. A 16-day-old breast fed infant with metabolic acidosis caused by salicylate. *Clin. Pediatr.*, 1981, **20**: 53-54.

17) Collins E. and Turner G. Fetal effects of regular salicylate ingestion in pregnancy. *Lancet.*, 1975, **2**: 338-339.

18) Corby D.G. and Schulman I. The effects of antenatal drug administration on aggregation of platelets of newborn infants. *Ped. Pharmacol. Therapeutics*, 1971, **79**: 307-313.

19) Davies M. and Marks R. Studies of salicylic acid on normal skin. *Br. J. Dermatol.*, 1976, **95**: 187.

20) Davies M.G., Vella Briffa D. and Greaves M.W. Systemic toxicity of topically applied salicylic acid. *Brit. Med. J.*, 1979, 661.

21) Davis, D.P. ?? *J. Pharm. Sci.*, 1997, **86**: 896-899.

22) Dekker G.A. and Sibai B.M. Low-dose aspirin in the prevention of preclampsia and fetal growth retardation: Rationale, mechanisms and clinical trials. *Am. J. Obstet. Gynecol.*, 1993, **168**: 214-227.

23) Di Sessa T.G., Moretti M.L., Khoury A. et al. Cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy. *Am. J. Gynecol.*, 1994, **171**: 891-900.

24) Done A.K. Salicylate intoxication: Significance of measurements of salicylate in blood in cases of acute ingestion. *Pediatrics*, 1960, **26**: 800-807.

25) Dubow E. and Soloman N.H. Salicylate tolerance and toxicity in children. *Pediatrics*, 1948, **1**: 495-504.

26) Elie R., Durocher L.P. and Kavalec E.C. Effect of salicylic acid on the activity of betamethasone-17,21-diproprionate in the treatment of erymatous squamous dermatoses. *J. Int. Med. Res.*, 1983, **11**: 108-112.

27) Eriksson M. and Larsson K.S. Salicylate induced foetal damage in two mouse strains: Studies on the distribution of 14C-labelled salicylic acid. *Acta Pharmacol. Toxicol.*, 1971, **29**: 256-264.

28) Ferguson R.K. and Boutros A.R. Death following self-poisoning with aspirin. *J. Am. Med. Assoc.*, 1970, **213**: 1186-1187.

29) Galea P. and Goel K.M. Salicylate poisoning in dermatological treatment . *Arch. Dis. Child*, 1989, **65**: 335.

30) Gilman A.G., Rall T.W., Nies A.S. and Taylor P. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eighth edition. *Pergamon Press New York*, 1990, 644-654.

31) Goldsmith L. Salicylic acid. *Int. J. Dermatol.*, 1979, **18**: 32-36.

32) Goodman L.S. and Gilman A. The pharmacological basis of therapeutics, Fourth Edition, The Mcmillan Co., 1970, New York.

33) Griffith J.F., Nixon G.A., Bruce R.D., Reer P.J. and Bannan E.A. Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. *Toxicol. Appl. Pharmacol.*, 1980, **55**: 501-513.

34) Harris R.M., Hawker R.J., Langman M.J., Singh S. and Waring R.H. Inhibition of phenolsulphotransferase by salicylic acid: a possible mechanism by which aspirin may reduce carcinogenesis.*Gut.*, 1998, **42**: 272-275.

35) Hartwig-Otto H. Pharmacokinetic considerations of common analgesics and antipyretics. *Am. J. Med.*, 1983, **75**: 30-37.

36) Hecht Y. Prevention of the side effects of aspirin with Maalox. *Med. Clin. Chir. Dig.*, 1981, **10**: 633-636.

37) Herz-Picciotto I., Hopenhayn-Rich C., Gloub M. et al. The risks and benefits of taking aspirin during pregnancy. *Epidemiologic. Rev.*, 1990, **12**: 108-148.

38) Heyman M.A. and Rudolph A.M. Effects od acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs utero. *Circ. Res.*, 1976, **38**: 418-422.

39) Huber C. and Christophers E. "Keratolytic" effect of salicylic acid. *Arch. Derm. Res.*, 1977, **257**: 293-297.

40) Ishidate MJr. Application of chromosomal aberration tests in vitro to the primary screening for chemicals with carcinogenic and/or genetic hazards. *Test Courts Cancerog. Quo Vadis (Symp)*, 1983, 57-79.

41) Johnson & Johnson, 12-day cumulative irritation,

42) Johnson & Johnson, 12-day cumulative irritation,

43) Johnson & Johnson, 14-day cumulative irritation,

44) Johnson & Johnson, HRIPT,

45) Johnson & Johnson, HRIPT,

46) Johnson & Johnson, HRIPT,

47) Johnson & Johnson, HRIPT,

48) Johnson & Johnson, HRIPT,

49) Johnson & Johnson, HRIPT,

50) Jongevos S.F., Prens E.P., Wolterbeek J.H. and Habets J.M. Acute perceptive hearing loss and metabolic acidosis as complications of the topical treatment of psoriasis with salicylic acid containing ointment. *Ned. Tijdschr. Geneeskd.*, 1997, **141**: 2075-2079.

51) Kaaja R., Julkunen H., Viinikka L. et al. Production of prostacylin and thromboxane in lupus pregnancies: Effect of a small dose of aspirin. *Obstet. Gynecol.*, 1993, **82**: 327-331.

52) Kaufman F.L. and Dubansky A.S. Darvon poisoning with delayed salicylism: a case report. *Pediatrics*, 1972, **49**: 610-611.

53) Kawachi T., Yahagi T., Kada T., Tazima Y. Ishidate M., Sasaki M.and Sugiyama T. Cooperative programme on short-term assays for carcinogenicity in Japan. In: Molecular and cellular aspects of carcinogen screening tests. Montesano R., Bartsch H. and Tomatis L. (eds.), International Agency for Research on Cancer, Lyon, France, 1979, 323-330.

54) Kimmel C.A., Wilson J.G. and Schumacher H.J. Studies on the metabolism and identification of the causative agent in aspirin teratogenesis in rats. *Teratology*, 1971, **4**: 15-24.

55) Kimmel C.A., Butcher R.E. and Vorhees C.V. Metal-salt potentiation of salicylate-induced teratogenesis and behavioral changes in rats. *Teratology*, 1974, **10**: 293-300.

56) King M.T., Beikirch H., Eckhardt K., Gocke E. and Wild D. Mutagenicity studies with X-ray contrast media, analgesics, antipyretics, antirrheumatics and some other pharmaceutical drugs in bacterial, Drosophila and mammalian test systems. *Mut. Res.*, 1979, **66**: 33-43.

57) LaDu B.N., Mandel H.G. and Way E.L. Fundamentals of drug metabolism and disposition. Baltimore, Williams and Wilkins, 1971, p182.

58) Levy G. and Tsuchiva T. Salicylate accumulation kinetics in man. *New Engl. Med. J.*, 1972, **287**: 430-432.

59) Levy G. and Garrettson K. Kinetics of salicylate eliminationby newborn infants of mothers who ingested aspirin before delivery. *Pediatrics*, 1974, **53**: 201-210.

60) Levy G. Clinical pharmacokinetics of aspirin. *Pediatrics*, 1978, **62**: 867-872.

61) Lewis R.B. and Schulman J.D. Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. *Lancet.*, 1973, **1**: 1159-1161.

62) Lukas D. Salicylic acid poisoning in infancy. *Arch, Kinderheilkd*, 1971, **82**: 168-174.

63) Lynd P.A., Andreasen A.C. and Wyatt R.J. Intrauterine salicylate intoxication in a newborn. *Clin. Pediatr.* 1976, **15**: 912-913.

64) Marchesi V.Y. and Andrews E.P. Glycoproteins: isolation from cell membranes with diiodosalicylate. *Science*, 1971, **174**: 1247.

65) Marks R., Davies M. and Cattell A. An explanation of the keratolytic effect of salicylic acid. *J. Invest. Dermatol.*, 1975, **64**: 283.

66) McCann J., Choi E., Yamasaki E. and Ames B.N. Detection of carcinogens as mutagens in Salmonella/microsome test: Assay of 300 chemicals. *Proc. Nat. Acad. Sci.*, 1975, **72**: 5135-5139.

67) McNeil J.R. The possible teratogenic effect of salicylates on the developing fetus. *Clin. Pediatr.*, 1973, **12**: 347-350.

68) Miller, C.G. and Pritchard, J.G. Current issues in NSAID therapy. Pharmacokinetics, *Prim. Care Phys.*, 1990, **17**: 589-601.

69) Mills D.G., Philip R.B. and Hirst M. The effects of some salicylate analogues on human blood platelets:1. Structure activity relationship and the inhibition of platelet aggregation. *Life Sci.*, 1974, **14**: 659-672.

70) Miners J.O. Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. *Clin. Pharmacokinet.*, 1989, **17**: 327-344.

71) Momma K. and Takeuchi H. Constriction of fetal ductus arteriosus by non-steriodal anti-inflammatory drugs. *Prostaglandins*, 1983, **26**: 631-643.

72) Moncada S. and Vale J.R. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A2, and prostacylicn, *Pharmacol. Rev.*, 1979, **30**: 293-334.

73) Nakatsuka T. and Fujii T. Comparative teratogenicity study of diflunisal and aspirin in the rat. *Oyo Yakuri*, 1979, **17**: 551-557.

74) Nater I.P. and De Groot S.C. Unwanted effects of cosmetics and drugs in dermatology, Elsevier 1985.

75) Nelson N.M. and Forfar J.O. Associations between drugs administered during pregnancy and congenitalo abnormalities of the fetus. *Brit. Med. J.*, 1971, **52**: 3527-3535.

76) O'Brien J.R. Effects of salicylate on humans platelets. *Lancet.*, 1968, **1**: 779-780.

77) Odashima S. Cooperative programme on long-term assays for carcinogenicity in Japan. In: Molecular and cellular aspects of carcinogen screening tests. Montesano R. Bartsch H. and Tomatis L. (eds.). International Agency for Research on Cancer, Lyon, France, 1979, 315-322.

78) Palmisano P.A. and Cassady G. Salicylate exposure in perinate. *J. Am. Med. Assoc.*, 1969, **209**: 556-558.

79) Pascher F. Systemic reactions to topically applied drugs. *Int. J. Dermatol.*, 1978, **17**: 768-775.

80) Patel D.K., Notarianni L.J. and Bennett P.N. Comparative metabolism of high doses of aspirin in rat and man. *Xenobiotica*, 1990, **20**: 847-854.

81) Paynter A.S. and Alexander F.W. Salicylate intoxication caused by teething ointment. *Lancet.*, 1979, **2**: 1132.

82) Procter & Gamble, Limit test for acute oral toxicity in rats, BCS0070, 1993a

83) Procter & Gamble, Limit test for acute oral toxicity in rats, BCS0025, 1993b

84) Procter & Gamble, Up/down procedure for an LD50, HBE BTS 0026, 1989a

85) Procter & Gamble, Acute percutaneous toxicity in rabbits, ECM BTS 206, 1976b

86) Procter & Gamble, Skin irritation study in guinea pigs, P81081, 1982a

87) Procter & Gamble, Skin irritation study in guinea pigs, P81069, 1982b

88) Procter & Gamble, Primary skin irritation study in rabbits, P79006, 1979a

89) Procter & Gamble, Skin irritation study in guinea pigs, P83012, 1983

90) Procter & Gamble, Primary skin irritation study in rabbits, BYCR0484, 1986

91) Procter & Gamble, Primary skin irritation/corrosion study in rabbits, ECM BTS 2085/02,
92) 1995a

93) Procter & Gamble, Primary skin irritation study in rabbits, P80027, 1980

94) Procter & Gamble, Primary skin irritation study in rabbits, P80087, 1982c

95) Procter & Gamble, Low volume eye irritation study in rabbits, BTS 0606/01, 1996

96) Procter & Gamble, Low volume eye irritation study in rabbits, BCS0070, 1993c

97) Procter & Gamble, Low volume eye irritation study in rabbits, BCS0025, 1993d

98) Procter & Gamble, Low volume eye irritation study in rabbits, SC 95A003, 1995b

99) Procter & Gamble, Low volume eye irritation study in rabbits, BCS0139, 1993e

100) Procter & Gamble, Low volume eye irritation study in rabbits, SC95A013, 1995c

101) Procter & Gamble, Low volume eye irritation study in rabbits, BS94A056-20, 1994a

102) Procter & Gamble, Low volume eye irritation study in rabbits, SC95A005, 1995d

103) Procter & Gamble, Low volume eye irritation study in rabbits, CS95A012, 1995e

104) Procter & Gamble, Low volume eye irritation study in rabbits, BD94A110-5G, 1995f

105) Procter & Gamble, Guinea pig closed patch test study, TGPSE 84, 1975

106) Procter & Gamble, Delayed contact hypersensitivity in guinea pigs, ECM BTS 206, 1976d

107) Procter & Gamble, Delayed contact hypersensitivity in guinea pigs, ECM BTS 206, 1976e

108) Procter & Gamble, Delayed contact hypersensitivity in guinea pigs, ECM BTS 206, 1976f

109) Procter & Gamble, In vitro skin penetration human skin, BCS0062(S3), 1994b

110) Procter & Gamble, 14-day percutaneous subchronic toxicity, BCS0062, 1993f

111) Procter & Gamble, 91-day subchronic percutaneous toxicity, IBSE0002, 1990a

112) Procter & Gamble, 91-day subchronic percutaneous toxicity, IBSE0001, 1990b

113) Procter & Gamble, 28-day percutaneous study, BCS0062S, 1994c

114) Procter & Gamble, 91-day subchronic percutaneous toxicity, BCS0062S, 1994d

115) Procter & Gamble, Perinatal toxicity study in rats, BCS0062(S2), 1994e

116) Procter & Gamble, Percutaneous pharmacokinetic study, BCS0099, 1994f

117) Procter & Gamble, Ocular irritancy evaluation study, CRL25895, 1995g

118) Procter & Gamble, Periocular application study, CR95010, 1995h

119) Procter & Gamble, Ophthalmologic safety evaluation study, SC95C016, 1995I

120) Procter & Gamble, HRIPT, IBSE0002, 1989b

121) Procter & Gamble, HRIPT, BTS 0028, 1988a

122) Procter & Gamble, HRIPT, BTS 1494, 1988b

123) Procter & Gamble, HRIPT, BTS 1493, 1988c

124) Procter & Gamble, HRIPT, BYCR1046/02, 1993g

125) Procter & Gamble, HRIPT, DRD 0030, 1993h

126) Procter & Gamble, HRIPT, BCS0025, 1993I

127) Procter & Gamble, HRIPT, HBE BTS 0327/01, 1993j

128) Procter & Gamble, HRIPT, BCS0070, 1993k

129) Procter & Gamble, HRIPT, BCS0105, 1995j

130) Procter & Gamble, HRIPT, SC95C014, 1995k

131) Procter & Gamble, HRIPT, SC95C015, 1995l

132) Procter & Gamble, HRIPT, SC95C002, 1995m

133) Procter & Gamble, HRIPT, SC95C008, 1995n

134) Procter & Gamble, HRIPT, CFTSE97/002, 1997

135) Procter & Gamble, 21-day cumulative irritation, BCS0133, 1993q

136) Procter & Gamble, 21-day cumulative irritation, BCS0025, 1993r

137) Procter & Gamble, 5-day cumulative cleanser, SC94C006, 1995r

138) Procter & Gamble, Back irritation, CR94037, 1995s

139) Procter & Gamble, Facial appearance/irritation, CR94062, 1994/5h

140) Procter & Gamble, Dermatologic safety evaluation, SC95C016, 1995v

141) Procter & Gamble, Facial appearance/irritation, CR93012, 1993s

142) Procter & Gamble, Facial appearance/irritation, BYCR 1046/03, 1993t

143) Procter & Gamble, 21-day cumulative irritation, BCS0093, 1993w

144) Procter & Gamble, 21-day cumulative irritation, BCS0093, 1993v

145) Procter & Gamble, HRIPT, BCS0080, 1993x

146) Procter & Gamble, HRIPT, BCS0138, 1994k

147) Procter & Gamble, 6-week facial irritation, BCS0070(S3), 1993z

148) Procter & Gamble, Dermatologic and ophtalmic safety study, SC95C037, 1996

149) Procter & Gamble, Periocular application study, CR95039, 1995z

150) Procter & Gamble, Periocular application study, 1995114, 1996b

151) Raschke R., Arnold-Capell P.A., Richeson R. and Curry S.C. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch. Intern. Med.*, 1991, **151**: 591-593.

152) Rasmussen J.E. and Fisher A.A. Allergic contact dermatitis to a salicylic acid plaster. *Contact Dermatitis*,1976, **2**: 237-238.

153) Richards G.D. Congenital malformations and environmental influences in pregnancy. *Brit. J. Prev. Soc. Med.*, 1969, **26**: 218-225.

154) Roberts D.L., Marshall R. and Marks R. Detection of the action of salicylic acid on the normal stratum corneum. *Brit. J. Dermatol.*, 1980, **103**: 191-196.

155) Roberts M.S. and Horlock E. Effect of repeated skin application on percuatenous absorption of salicylic acid. *J. Pharm. Sci.*, 1978, **67**: 1685-1687.

156) Robinson M.K., Nusair T.L., Fletcher E.R. and Ritz H.L. A review of the Buehler guinea pig skin sensitization test and its use in a risk assessment process for human skin sensitization. *Toxicology*, 1990, **61**: 91-107.

157) Roth G.J. and Siok C.J. Acetylation of the NH2-terminal serine of prostaglandin synthetase by aspirin. *J. Biol. Chem.*, 1978, **253**: 3782-3784.

158) Settipane G.A. Aspirin and allergic diseases: a review. *Am. J. Med.*, 1983, **74**: 102-109.

159) Shapiro S., Siskind V., Monson R.R., Heinonen O.P., Kaufman D.W. and Slone D. Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. *Lancet.*, 1976, **1**: 1375-1376.

160) Shaw G.M. Malcoe L.H., Swan S.H. Cummins S.K., Schulman J. and Harris J.A. Risks for congenital cardiac anomalies relative to selected maternal exposures during early pregnancy. *Teratology*, 1990, **41**: 590.

161) Slone D., Heinonen O.P., Kaufman D.W., Siskind V., Monson R.R., Shapiro S. Aspirin and congenital malformations. *Lancet.*, 1976, **1**: 1373-1374.

162) Smith W.O. and Lyons D. Metabolic acidosis associated with percutaneous absorption of salicylic acid. *J. Okla. State Med. Assoc.*, 1980, **73**: 7-8.

163) Steele K., Shirodaria P., O'Hare M. Monochloracetic acid and 60% salicylic acid as treatment for simple plantar warts: effectiveness and mode of action. *Br. J. Dermatol.*, 1988, **118**: 537-544.

164) Stich H.F., Rosin M.P. Wu C.H. and Powrie W.D. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. *Cancer Lett.*, 1981, **14**: 251-260

165) Stolar M.E., Rossi V.G. and Barr M. The effect of various bases on the percutaneous absorption of salicylate I. Effect of type of ointment base. *J. Amer. Pharm. Assoc.*, 1960, **49**: 144-147.

166) Tanaka S., Kawashima K, Nakaura S., Nagao S., Kuwamura T., Takanaka A. and Omori Y. Studies on teratogenic effects of salicylic acid and aspirin in rats as related to fetal distribution. *Congenital Abnormalities*, 1973, **13**: 73-84.

167) Tanaka S., Kawashima K., Nakaura S. Nagao S., Kuwamura T., Takanaka A. and Omori Y. Teratogenic effect of dietary salicylic acid in rats. *J. Food. Hyg. Soc.*, 1973, **14**: 549-557.

168) Taylor J.R. and Halprin K.M. Percutaneous absorption of salicylic acid. *Arch. Dermatol.*, 1975, **111**: 740-743.

169) Thomas B.H., Nera E.A. and Zeitz W. Failure to observe pathology in the rat following chronic dosing with acetaminophen and acetylsalicylic acid. *Res. Commun. Chem. Pathol. Pharmacol.*, 1977, **17**: 663-678.

170) Thun M.J., Namboodiri M.M.and Heath C.W. Aspirin use and reduced risk of fatal colon cancer. *N. Engl. J. Med.*, 1991, **325**: 1593-1596.

171) Tikkanen J. and Heinonen O.P. Congenital heart disease in the offspring and maternal habits and home exposures during pregnancy. *Teratology*, 1992, **46**: 447-454.

172) Trasler D.G. Aspirin induced cleft lip formation and other malformations in mice. *Lancet.*, 1965, **1**: 606-607.

173) Tuchman-Duplessis H., Hiss D., Mottot G. and Rosner I. Effects of prenatal administration of acetylsalicylic acid in rats. *Toxicology*, 1975, **3**: 207-211.

174) Turner G. and Collins E. Fetal effects of regular salicylate ingestion in pregnancy. *Lancet.*, 1975, **1**: 338-339.

175) Von Weiss J.F. and Lever W.F. Percutaneous salicylic acid intoxication in psoriasis. *Arch. Dermatol.*, 1964, **90**: 614-619.

176) Warknay J. and Takacas E. Experimental production of congenital malformations in rats by salicylate poisoning. *Amer. J. Path.*, 1959, **35**: 315-331.

177) Washitake M., Anmo T., Tanaka I., Arita T., and Nakano M. Pecutaneous absorption of drugs IV: Percutaneous absorption of drugs from oily vehicles. *J. Pharmaceut. Sci.*, 1975, **64**: 397-401.

178) Weigert S.R., Gorisch V. and C. Kluge. Percutaneous salicylic acid poisoning in infancy. *Arztl. Fortbild. Jena*, 1978, **72**: 427-432.

179) Weirich E.G. Dermatopharmacology of salicylic acid. I. Range of dermatotherapeutic effects of salicylic acid. *Dermatologica*, 1975, **151**: 268-273.

180) Werler M.M., Mitchell A.A. and Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N. Engl. J. Med.*, 1989, **321**: 1639-1642.

181) Wilson J.G. Use of rhesus monkeys in teratological studies. *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 1971, **30**: 104-109.

182) Wilson J.G., Scott W.J. and Ritters E.S.. Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats and rhesus monkeys. *Toxicol. Appl. Pharm.*, 1977, **41**: 67-78.

183) Young C.J. Salicylate intoxication from cutaneous absorption of salicylic acid. *Southern Med. J.*, 1952, **45**: 1075-1077.

184) Yu H.Y., Shen Y.Z., Sugiyama Y. and Hanano M. Drug interaction. Effects of salicylate on pharmacokinetics of valproic acid in rats. *Drug. Metabol. Dispos.*, 1990, **18**: 121-126.

185) Zetterberg G. Mechanism of the lethal and mutagenic effects of phenoxyacetic acids in *Saccharomyces cerevisiae*. *Mutat. Res.*, 1979, **60**: 291-300.

186) Zierler S. and Rothman K.J. Congenital heart disease in relation to maternal use of bendectin and other drugs during early pregnancy. *N. Engl. J. Med.*, 1985, **313**: 347-352.

APPENDIX I: EXPOSURE ASSESSMENT

In its most recent revision to the "Notes of Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation" the SCCNFP presents a worst-case scenario for the global consumer exposure to cosmetics. From this, a total topical exposure to cosmetics potentially containing salicylic acid is estimated to be 17.74 g/day.

In the case of evaluation of a new preservative for the positive list, exposure is calculated based on the assumption that the substance is present in all cosmetic products at the maximum requested concentration. If, indeed, all product types were to contain salicylic acid as a preservative at the maximum allowed level of 0.5 %, topical exposure to salicylic acid would be 89 mg/day. The SCCNFP Notes of Guidance acknowledge that this exposure scenario is exaggerated and such *"extreme values would not be reached in practice"*.

Exposure to "other uses" is calculated from the table presented in Annex V of the SCCNFP Guidelines. For each individual product type, the allowed preservative concentration (0.5%) is replaced by the "other use concentration".

Overall exposure (preservative and potential "other uses") should not be carried out by taking the exaggerated preservative exposure as the starting point, and replacing the preservative concentration by the "other use" concentration for all concerned product types. Under this approach, total consumer exposure (topical) to salicylic acid would be estimated from the **concomitant daily use of :**

- ✓ a 2% salicylic acid-containing face cream,
- ✓ a 2% salicylic acid-containing general (hand) cream,
- ✓ a 1 % salicylic acid-containing leave-on hair product,
- ✓ all rinse-off products containing 2% salicylic acid
- ✓ all remaining cosmetic products containing 0.5% salicylic acid.

This obviously adds to the already existing overestimation of exposure, especially for an ingredient such as salicylic acid, which is not widely used in cosmetics. In a more realistic (but still exaggerated manner) overall exposure could be carried out by taking the exaggerated preservative exposure as the starting point, and replacing the preservative concentration by the "other use" concentration for the product types which gives the highest exposure. Following this approach, total consumer exposure (topical) to salicylic acid would be estimated from the concomitant daily use of :

- ✓ a 2% salicylic acid-containing general (hand) cream,
- ✓ all other cosmetic products containing 0.5% salicylic acid.

Topical exposure would be estimated to be 165 mg/day from the first exposure scenario and 125 mg/day from the more realistic scenario.

Considering 20 % percutaneous absorption, systemic exposure would be estimated to be 0.4 mg/kg b.w./day for a 60 kg person. (0.6 mg/kg b.w./day for the highly exaggerated scenario).

Serum levels

It has been shown that topical administration of 25 mg salicylic acid results in serum levels of 0.27-0.5 µg/ml (Procter & Gamble, 1994f). Based on this study, and assuming linear relationship between amount of salicylic acid applied and serum levels achieved, the serum levels resulting from the estimated systemic exposure can be calculated as:

Amount of salicylic acid applied topically: 125 mg/day

Serum levels: (125 x 0.5) / 25 = 2.5 µg/ml (= 0.25 mg/ 100 ml)

APPENDIX II: MARGIN OF SAFETY

Systemic toxicity

Subchronic percutaneous toxicity studies in rabbits have shown that the effect of salicylic acid up to 120 mg/kg/day (the highest dose tested) was limited to dermal irritation. This exposure is 58 times higher than the expected exposure to salicylic acid from the consumer scenario.

In humans, plasma salicylate levels required for systemic effects range between 46 and 64 mg/100 ml over a course of 3-10 days. These levels are at least 184 times higher than those estimated from topical application of cosmetic products containing salicylic acid of 0.25 mg/100 ml.

Reproductive toxicity and Teratogenicity

The NOAEL of sodium salicylate when administered orally to mated rats was 80 mg/kg/day with regard to maternal toxicity and developmental toxicity. The systemic exposure from salicylic acid-containing cosmetic products under the worst-case scenario conditions (i.e. 0.4 mg/kg/day) is therefore 200 timers lower than the NOAEL.

In rats, a LOEL of 75 mg/kg/day has been reported for salicylate-related teratogenic effects. However, the NOEL in the non-human primate model is 100 mg/kg/day, given their lower susceptibility to salicylate-induced fetotoxicity and teratogenicity. The systemic exposure from salicylic acid-containing cosmetic products under the worst-case scenario conditions (i.e. 0.4 mg/kg/day) is 250 timers lower than the reported NOEL in the monkey studies.

In humans, at low therapeutic doses (60-150 mg/day, orally), large prospective studies have found no evidence that acetylsalicylic acid consumption during pregnancy leads to congenital malformations or the appearance of ductus artheriosus. These oral low therapeutic doses are estimated to result in serum levels up to 0.93 mg/100 ml and are higher than those estimated for the exposure to salicylic acid-containing cosmetic products under the consumer scenario of 0.25 mg/100 ml. Clinical incidence of acetylsalicylic acid-related increases in labor gestation times and postpartum hemorrhaging have only been noted at doses of 3200 mg/day in patients with musculoskeletal disorders (estimated serum levels 20 mg/100 ml). Importantly, these human data have been obtained in clinical studies conducted with acetylsalicylic acid. Considering the reversible activity of salicylic acid in inhibiting the prostaglandin synthesis and its clinical inefficiency when compared to acetylsalicylic acid, this margin of safety should be considered very conservative.

Proposed Rulemaking for the Treatment of Dandruff, Seborrheic dermatitis, Psoriasis

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may increase your tendency to sunburn for up to 24 hours after application."

(b) "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor."

References

(1) Downing, J. G., and C. W. Bauer, "Low and High Temperature Coal Tars in the Treatment of Eczema and Psoriasis. A Clinical Investigation and Evaluation," *Archives of Dermatology and Syphilology*, 57:985–990, 1948.

(2) "The United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 161, 1980.

(3) Grupper, C., "The Chemistry, Pharmacology, and Use of Tar in the Treatment of Psoriasis," *in* "Psoriasis, Proceedings of the International Symposium," edited by E. M. Farber and A. J. Cox, Stanford University Press, Stanford, CA, pp. 347–356, 1971.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 128, 1976.

(5) Rasumssen, J. E., "The Crudeness of Coal Tar," *Progress in Dermatology*, 12:23–29, 1978.

(6) Summary Minutes of the 19th meeting of the Advisory Review Panel on Miscellaneous External Drug Products, June 25, 1977.

(7) Obermayer, M. E., and S. W. Becker, "A Study of Crude Coal Tar and Allied Substances—Preliminary Report," *Archives of Dermatology and Syphilology*, 31:796–810, 1935.

(8) Nelson, M. O., and A. E. Osterberg, "A Purified Coal Tar Ointment for the Treatment of Infantile Eczema," *Archives of Dermatology and Syphilology*, 15:669–671, 1927.

(9) Jaffrey, W. R., "A Report on the Therapeutically Active Principle Fraction of Crude Coal-Tar," *The Canadian Medical Association Journal*, 18:680–681, 1928.

(10) Osol, A., editor, "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, p. 724, 1980.

(11) OTC Volume 160051.

(12) OTC Volume 160253.

(13) OTC Volume 160325.

(14) OTC Volume 160327.

(15) Muller, S. A., and R. R. Kierland, "Crude Coal Tar in Dermatologic Therapy," *Mayo Clinic Proceedings*, 80:275–280, 1964.

(16) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Van Nostrand Reinhold, New York, p. 576–577, 1968.

(17) Muller, S. A., and R. R. Kierland, "Crude Coal Tar Dermatologic Therapy," *Mayo Clinic Proceedings*, 34:275–280, 1964.

(18) Herxheimer, A., "Drugs Used in the Treatment of Skin Diseases," *in* "Side Effects of Drugs," edited by L. Meyler and A. Herxheimer, The Williams and Wilkins Co., Baltimore, p. 185, 1968.

(19) Kaidbey, K. H., and A. M. Kligman, "Topical Photosensitizers—Influence of Vehicles on Penetration," *Archives of Dermatology*, 110:868–870, 1974.

(20) Burckhardt, W., and P. Schmid, "Das Licht als Pathogene Noxe," *Schweizerische Medizinische Wochenschrift*, 99:439–444, 1969.

(21) Hoffman, D., "Coal Tar Carcinogenicity Studies," presented at the Coal Tar Symposium, Food and Drug Administration, Washington, June 25, 1977.

(22) Horton, W. A., "An Investigation of the Carcinogenic Properties of Various Coal Tars or Commercial Fractions Thereof," Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, March 17, 1961.

(23) Wallcave, H., et al., "Skin Tumorigenesis in Mice by Petroleum Asphalts and Coal-Tar Pitches of Known Polynuclear Aromatic Hydrocarbon Content," *Toxicology and Applied Pharmacology*, 18:41–52, 1971.

(24) Hilfrich, J., and U. Mohr, "Vergleichende Untersuchungen zur Carcinogenen Wirkung des herkommlichen Steinkohlenteers und einer neuen synthetischen Teermischung," *Archiv fur Dermatologische-forschung*, 242:176–178, 1972.

(25) Pott, P. "Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum, the Different Kinds of Ruptures, and the Mortification of the Toes and Feet," L. Hawes, W. Clarke, and R. Collins, London, pp. 63–68, 1775.

(26) Greither, A., C. Gisbertz, and H. Ippen, "Teerbehandlung und Krebs," *Zeitschrift fur Haut-geschlechts-Krankheiten 42*, 15:631–635, 1967.

(27) Maughn, W. Z., et al., "Incindence of Skin Cancers In Patients With Atopic Dermatitis Treated With Coal Tar," *Journal of the American Academy of Dermatology*, 3:612–615, 1980.

(28) Farber, E. M., editor, "International Psoriasis Bulletin," 4:1–6, Stanford University, Stanford, CA, 1977.

(29) Silver, H., E. S. Bereston, and M. J. Scham, "Hydrotherapeutic Action of Crude Coal Tar in Selected Dermatoses," *New York State Journal of Medicine*, 55:1724–1727, 1955.

(30) Combes, F. C., "The Use of Coal Tar in the Treatment of Skin Diseases," *The New England Journal of Medicine*, 228:384–386, 1943.

(31) Lerner, M. R., and A. B. Lerner, "Tar Preparations," *in* Dermatologic Medications," 2d Ed., Year Book Publishers, Chicago, pp. 168–170, 1960.

(32) Berman, A., "Coal Tar Products," *Bulletin of the American Society of Hospital Pharmacists*, 5:100–104, 1948.

(33) Olansky, S., "Whole Coal Tar Shampoo: A Therapeutic Hair Repair System," *CUTIS: Cutaneous Medicine for the Practitioner*, 25:99–104, 1980.

(34) Combes, F. C., "Coal Tar in Dermatology—An Improvement in its Physical Properties Without Any Change in Its Therapeutic Action," *Archives of Dermatology and Syphilology*, 56:583–588, 1947.

(35) Gruber, M., R. Klein, and M. Foxx, "Chemical Standardization and Quality Assurance of Whole Crude Coal Tar USP Utilizing GLC Procedures," *Journal of Pharmaceutical Sciences*, 59:830–834, 1970.

(36) OTC Volume 160314.

(37) Statistical evaluation solicited by the Advisory Review Panel on OTC Miscellaneous External Drug Products from R. B. D'Agostino, OTC Volume 160438.

(38) OTC Volume 160387.

(39) OTC Volume 160314.

(40) OTC Volume 160129.

(41) OTC Volume 160241.

(42) OTC Volume 160237.

(43) OTC Volume 160379.

(44) OTC Volume 160305.

(45) OTC Volume 160307.

(46) OTC Volume 160316.

(47) OTC Volume 160364.

(48) Parish, C. L., and J. A. Witowski, "Pityriasis, Seborrheic Dermatitis, and Dandruff: Evaluation of a Tar Shampoo," *CUTIS: Cutaneous Medicine for the Practitioner*, 14:257–259, 1974.

(49) OTC Volume 160375.

(50) Young, E., "The External Treatment of Psoriasis. A Controlled Investigation of the Effects of Coal Tar," *British Journal of Dermatology*, 82:510–515, 1970.

b. *Salicylic acid.* The Panel concludes that salicylic acid is safe and effective for OTC topical use for controlling seborrheic dermatitis of the body and scalp, psoriasis of the body and scalp, and dandruff.

Salicylic acid (2-hydroxybenzoic acid) occurs as acicular crystals or as a crystalline powder. It is found principally in wintergreen leaves and in the bark of sweet birch, can be made synthetically, and gradually discolors in sunlight. One gram (g) is soluble in 460 mL water, 3 mL acetone, 2.7 mL alcohol, 42 mL chloroform, 3 mL ether, about 60 mL glycerol, and 52 mL oil of turpentine. The pH of a saturated aqueous solution is 2.4. It is used topically mainly for its keratoplastic activity (correction of abnormal keratinization) in low concentrations, its keratolytic activity (causing peeling of the skin) in higher concentrations, and its antifungal and antibacterial activities (Ref. 1).

(1) *Safety.* Salicylic acid and its derivatives are used as analgesics, antipyretics, fungistatics, keratolytics, rubefacients, and anti-inflammatory agents.

Salicylic acid softens and destroys the stratum corneum by increasing water concentration, probably as a result of lowering the pH, which causes the horny layer of the skin to swell, soften, and then shed. Damage to normal skin has been associated with its overuse.

Systemically, salicylic acid and its compounds produce a variety of reactions in man which are collectively called "salicylism." The early symptoms of salicylism, which may begin when the plasma salicylate level is as low as 12.2 mg/100 mL, are erythema, ringing in the ears, deafness, nausea, and vomiting. The more severe reactions, which may appear when the plasma salicylate levels range from 40 to 50 mg/100 mL, include severe drowsiness, confusion,

euphoria, difficulty in breathing, and hemorrhage (Ref. 2).

The Panel notes that OTC products containing salicylic acid for the control of dandruff, seborrheic dermatitis, and psoriasis are marketed in concentrations varying from 1.8 to 3 percent. The Panel concludes that, because of the relatively weak concentration and the method of use of these products, there is no potential for toxic effects to occur from percutaneous absorption.

(2) *Effectiveness.* Most salicylic acid products on the OTC market for topical use contain this ingredient in combination with other ingredients (Refs. 3 through 21). Consequently, few studies have been conducted on salicylic acid as a single ingredient for topical use.

The Panel is aware of a recent double-blind study in which 2 percent salicylic acid, 2 percent sulfur, and a combination of sulfur and salicylic acid (2 percent each) were tested against a vehicle for controlling dandruff (Ref. 3). Forty-eight subjects were included in the 5-week study. The products were used under supervision twice a week. Clinical grading of dandruff was on a scale from 0 to 10, and weekly corneocyte counts were made. A significant reduction in both the clinical grade of scaling and corneocyte count was reported for salicylic acid as compared to the vehicle control.

The Panel is aware of only one other study in which salicylic acid was evaluated as a single ingredient in the control of dandruff (Ref. 4). Four different preparations were included in the study: 2 percent sulfur in combination with 2 percent salicylic acid, 2 percent sulfur in combination with 2 percent salicylic acid in a protein formulation, 2 percent sulfur combined with 2 percent salicylic acid and 0.5 percent coal tar, and 1.8 percent salicylic acid in a lotion vehicle intended for daily application. Ten subjects with a minimum degree of scaling (score of 5 or greater on a 10-point scale) were assigned to each formulation. Evaluations were made at 3 and 6 weeks. The study demonstrated that the salicylic acid lotion preparation showed statistically significant reductions in both clinical grade and corneocyte counts at both 3 and 6 weeks.

All other studies reviewed by the Panel were conducted using salicylic acid in combination with other ingredients (Refs. 5 through 21). The Panel's evaluations of combination products are discussed elsewhere in this document. (See part III. paragraph D. below—Combination Products.) Although the studies mentioned above were limited to concentrations of 2 percent salicylic acid, the agency recognizes that products submitted to the Panel for review contained from 1.8 to 3 percent salicylic acid. The Panel previously reviewed salicylic acid in its report on OTC corn and callus remover drug products published in the **Federal Register** of January 5, 1982 (47 FR 522) and concluded that at concentrations above 1 percent this ingredient has keratolytic action on the skin. Because the effect of salicylic acid in dandruff, seborrheic dermatitis, and psoriasis is due to its keratolytic action in removing scales, the Panel concludes that salicylic acid is effective for controlling seborrheic dermatitis and psoriasis of the body and scalp and dandruff.

(3) *Dosage.* For topical use in concentrations of 1.8 to 3 percent.

(4) *Labeling.* The Panel recommends the Category I labeling described below. (See part III. paragraph A.2. below—*Category I labeling.*)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1080, 1976.

(2) Graham, J. D. P., and W. A. Parker, "The Toxic Manifestations of Sodium Salicylate Therapy," *Quarterly Journal of Medicine*, 17:153–163, 1948.

(3) OTC Volume 160414.
(4) OTC Volume 160397.
(5) OTC Volume 160069.
(6) OTC Volume 160070.
(7) OTC Volume 160299.
(8) OTC Volume 160309.
(9) OTC Volume 160314.
(10) OTC Volume 160316.
(11) OTC Volume 160318.
(12) OTC Volume 160320.
(13) OTC Volume 160323.
(14) OTC Volume 160324.
(15) OTC Volume 160325.
(16) OTC Volume 160327.
(17) OTC Volume 160356.
(18) OTC Volume 160379.
(19) OTC Volume 160397.
(20) OTC Volume 160241.
(21) OTC Volume 160406.

c. *Selenium sulfide.* The Panel concludes that selenium sulfide is safe and effective for OTC topical use for controlling dandruff.

Selenium sulfide, also referred to as selenium disulfide, is a bright orange powder prepared from selenious acid and hydrogen sulfide (Ref. 1). It is practically insoluble in water and organic solvents, but soluble in carbon disulfide and benzene (Refs. 1 and 2). Selenium is an essential trace element for man and is contained in the enzyme glutathione peroxidase (Ref. 3).

Selenium sulfide is used in OTC detergent suspension shampoos in a 1-percent concentration for controlling dandruff (Ref. 4). Presently this ingredient is marketed for control of seborrheic dermatitis only in a 2.5-percent concentration that is restricted to prescription use. The Panel knows of no studies that have been done to demonstrate the effectiveness of a 1-percent concentration in controlling seborrheic dermatitis, but suggests that manufacturers might wish to consider performing such studies to determine whether the lower concentration is in fact effective for controlling seborrheic dermatitis as well as dandruff.

(1) *Safety.* Because selenium sulfide is practically insoluble in water and organic solvents, its toxicity contrasts sharply with the highly toxic water-soluble selenium compounds and with elemental selenium. The oral LD_{50} for selenium sulfide in rats is 138 mg/kg, as compared to 7 mg/kg for highly soluble sodium selenite. Available evidence indicates that there is little danger of absorbing toxic amounts when selenium sulfide is applied to normal intact skin or hair (Ref. 5). This ingredient has been used in an OTC antidandruff shampoo in a concentration of 1 percent for several years with very few reported incidences of toxicity.

A series of four studies was done to determine whether selenium was absorbed through intact skin on the scalp as a result of shampooing under normal conditions with a 1-percent selenium sulfide shampoo (Ref. 4). The first two studies were designed to determine when peak blood levels would occur if any selenium were absorbed. In the first study, blood samples were drawn from four subjects 12 hours after shampooing, and urinary excretion of selenium was measured over a period of 24 hours following use of the shampoo. In the second study, blood samples were drawn from four subjects 4 hours after shampooing, 8 hours after shampooing, and at intervals in between. Measurements of selenium excreted in urine were made five times over a 24-hour period. Apparently no selenium was absorbed because there appeared to be no change in blood selenium levels other than slight variations that were within the standard deviation of the analytical method.

The third study was conducted on four subjects who shampooed with the 1-percent selenium sulfide preparation twice a week for 8.5 weeks. Simultaneously, a control group of four subjects used a shampoo that did not contain selenium sulfide, and blood and urine selenium levels were measured in both groups. The difference in blood selenium levels and urine selenium levels between control and experimental subjects was neither statistically nor

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a lipid-soluble drug; 1 gram (g) dissolves in approximately 460 milliliters (mL) water or 15 mL boiling water, 2.7 mL alcohol, 3 mL acetone, 42 mL chloroform, 3 mL ether, 135 mL benzene, 52 mL turpentine, 60 mL glycerin, or 80 mL of fats or oils which makes salicylic acid compatible with a variety of pharmaceutical vehicles (Ref. *1*).

a. *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. They are used as analygesics (pain relievers), antipyretics (fever reducers), keratolytics (peeling agents), rubefacients (agents that cause reddening of the skin), and anti-inflammtory agents. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. When salicylates are administered in a toxic dose, the potential side effects are nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and, in some extreme cases, death. These toxic reactions are collectively known as salicylism. However, the Panel is unaware of any report of salicylism resulting from the topical use of salicylic acid as a corn and callus remover.

Salicylic acid, when used topically in concentrations of 1 percent and higher, depending on the vehicle, is keratolytic on normal skin and should be applied carefully to hyperkeratotic areas of skin to avoid damage to adjacent healthy skin. It softens and destroys the outer layer of skin by increasing endogenous hydration (water concentration) in this area. This action probably results from lowering the pH and causes the cornified epithelium (horny skin) to swell, soften, and then shed. Necrosis (cell death) of the normal skin has been associated with overuse of salicylic acid (Ref. *2*).

A primary dermal irritation study (Ref. *3*) using a 14-percent concentration of salicylic acid in both acetone collodion and collodion vehicles was performed using the standard Draize Irritation Test on six albino New Zealand rabbits. The procedure for using both test solutions was the same. Application of 0.5 mL of the test material was made to clipped areas of intact and abraded skin. Following application of the test material, the entire trunk of each animal was covered with an impermeable occlusive wrapping. The wrapping and test material were removed and discarded at the end of 24 hours. The skin was examined at 24 and 72 hours following application.

On a scale of 0 to 5, the results of the study showed that 14 percent salicylic acid in acetone collodion gave a primary irritation index of 0.25 (potential for slight irritation, rarely irritating to people, no warning required). Fourteen-percent salicylic acid in collodion gave a primary irritation index of 1.0 (potential for mild irritation, possibly irritating to some people under occlusive wrap conditions, usually no warning required).

A midwestern research department in podiatric medicine conducted two investigations to determine the safety of OTC corn removers containing salicylic acid (Ref. *4*). The first retrospective investigation in September 1976 used completed outpatient medical records for the same year 1974 as a data base. The second investigation, conducted for one week in September 1977, was aimed at the collection of specific and current information on this subject through in-depth interviews. A specifically designed questionnaire was employed as the instrument of the survey and was conducted by a team of doctors on a cross section of the population of Chicago.

The results of the first investigation showed that, of the 3,165 patients who visited the foot clinic in 1974, 2,140 (67.6 percent) were identified as having corns and calluses. A team of researchers carefully examined the clinical histories of each record. A specific search was made for instances where the use of corn removers containing salicylic acid could have been the cause of the clinic visit in 1974. No cases were recorded.

The results of the patient interview survey showed that, out of a total of 953 patients who visited the clinic during the week of the survey, 604 (63.4 percent) had been diagnosed as having corns and calluses. Seventy-two (12 percent) of those 604 patients gave histories of self-medication through the application of corn removers containing salicylic acid. None of the users of such products complained of ever having an adverse reaction which became so severe, in the judgment of the patient, as to necessitate treatment by a doctor. The researchers concluded that there was a complete absence of serious side effects in the cases studied as a result of self-treatment with corn removers containing salicylic acid. This conclusion, in addition to the history of repeated use of such products by many of the patients seen, indicated to the researchers that the application of corn removers containing salicylic acid was safe.

b. *Effectiveness.* Salicylic acid is commonly used by the consumer in OTC preparations for its peeling action in the treatment of hyperkeratotic conditions such as corns and calluses. It is usually formulated in flexible collodion, plasters, disks, or pads.

Flexible collodion contains pyroxylin in a mixture of ether and alcohol, and plasticizers (camphor and castor oil). Pyroxylin is a nitrocellulose derivative which, after evaporation of the volatile solvents, remains on the skin as an insoluble water-repellant film that adhers better than an aqueous system (Ref. *5*). Flexible collodion is highly flammable and therefore must be stored at room temperature away from heat and must be kept away from fire or flame. Care must also be taken to keep the bottle tightly capped to avoid rapid evaporation of the product and inhalation of the volatile solvents which may cause hypnotic or other undesirable effects.

Collodion, plaster, disk, and pad dosage forms are advantageous because they are adherent and assure contact of the medication with the affected area (Ref. *6*). They also prevent moisture evaporation from the skin, and thereby facilitate penetration of the active ingredient into the affected area resulting in sustained local action of the drug.

Moisture is essential for salicylic acid to exert its action and for maceration and desquamation of epidermal tissue to take place. For that reason, soaking the feet for 15 to 30 minutes and drying before applying the medication aids the keratolytic action of salicylic acid.

A double-blind study was conducted to determine the safety and effectiveness of medicated disks containing 40 percent salicylic acid for the removal of corns and calluses (Ref *7*). Of the 73 male and female subjects recruited for the study, 54 met the baseline requirements, and 51 completed the study. Subjects were selected for the study if they had at least two lesions, either corns or calluses.

The lesions were classified, graded clinically, measured in size, and rated for pain sensation. Lesions were grouped into pairs. Treatments of active drug and placebo were randomly assigned and applied in a double blind fashion. Of the 52 corns and 68 calluses studied, 26 corns and 34 calluses were treated with medicated disks, and the remaining one-half were treated with placebo disks. A total of five applications including the initial application were made in 11 days (at 48 and 72-hour intervals). During each visit the disk was removed, the lesions evaluated, and another disk applied.

The results of the study showed that 19 of the 26 (73 percent) corns treated with the active drug were completely removed as opposed to 1 of 26 (4 percent) treated with the placebo which was a significant difference. In

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October 3, 1980

publication of the final monograph in the Federal Register.

Category I ingredient

Salicylic acid. The Panel concludes that salicylic acid is safe and effective for OTC use as a wart remover active ingredient in OTC topical drug products when used within the dosage limits specified in the dosage section stated below.

Salicylic acid, also known as 2-hydroxybenzoic acid and *o*-hydroxybenzoic acid, is found in nature in wintergreen leaves and in the bark of the sweet birch. It is synthesized by heating sodium phenolate with carbon dioxide under pressure. Salicylic acid is a lipid-soluble drug. One gram (g) dissolves in approximately 460 milliliters (mL) water or 15 mL boiling water, 2.7 mL alcohol, 3 mL acetone, 42 mL chloroform, 3 mL ether, 135 mL benzene, 52 mL oil turpentine, about 60 mL glycerol, or about 80 mL of fats or oils, which makes salicylic acid compatible with a variety of pharmaceutical vehicles (Ref. 1). The melting point is between 157° and 159° C.

The mechanical removal of epidermal cells infected with wart viruses is dependent on the keratolytic (peeling) effect of salicylic acid. The induction of an inflammatory reaction promotes disappearance of a wart possibly by the immune mechanisms (Ref. 2).

a. *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. They are used as analgesics (relieving pain), antipyretics (relieving fever), fungistatics (inhibiting fungi growth), keratolytics (peeling), rubefacients (reddening the skin), and have anti-inflammatory effects. Systemic absorption occurs whether the salicylates are administered orally, rectally, intravenously, or cutaneously. Whatever the mode of administration, the potential side effects of a doxic dose are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and, in some extreme cases, death. These possible toxic reactions are collectively known as salicylism. The Panel is unaware of any report of salicylism occurring from the cutaneous use of salicylic acid as a wart remover.

Long-term use of salicylic acid in concentrations as low as 1 percent in petrolatum may cause damage on normal skin (Ref. 3). Salicylic acid softens and destroys the stratum corneum (outer layer of skin) by increasing endogenous hydration (water concentration), probably as a result of lowering the pH which causes the cornified epithelium (horny skin) to swell, soften, and then desquamate (shed). Damage and necrosis (cell death) of the normal skin have been associated with overuse.

A primary dermal (skin) irritation study using a 14-percent salicylic acid concentration in acetone collodion was performed using the standard Draize Irritation Test on white rabbits. The solution (0.5 mL) was applied to intact skin and abraded skin of six shaved albino rabbits. The test areas were covered by occlusive patches. The rabbits were observed at 24 and 72 hours. A 14-percent salicylic acid concentration in acetone collodion was found to be minimally irritating with a primary irritation factor of 0.25 on a scale ranging from 0 (no irritation) to 5.0 (corrosive). a 14-percent concentration of salicylic acid in collodion yielded a primary irritation factor of 1.0 (slightly irritating) (Ref. 4).

Rate of removal of warts is not as important as the safety in their removal. The use of concentrations as low as 1 percent salicylic acid for a long period of treatment is safer than the use of higher concentrations greater than 17 percent for a short period of time. The Panel concludes that due to the extreme keratolytic effect of salicylic acid, use of a concentration of salicylic acid higher than 17 percent to treat common or planter warts should be under the supervision of a doctor.

b. *Effectiveness.* Textbooks cite the longstanding use of salicylic acid preparations in the treatment of warts (Refs. 5 through 10). The therapeutic effectiveness of salicylic acid in wart therapy depends upon the presence of moisture; therefore, salicylic acid is usually incorporated into vehicles (plasters, flexible collodions, occlusive ointments) that occlude the area and promote hydration (taking up of water), causing maceration of the skin.

Salicyclic acid used in the treatment of warts is usually formulated in flexible collodion. This vehicle contains pyroxylin, volatile solvents (ether, acetone, or alcohol), and plasticizers (camphor and castor oil). Pyroxylin is a nitrocellulose derivative, which after evaporation of the volatile solvents remains on the skin as an insoluble water-repellent film that is less likely to spread beyond the area applied than an aqueous system (Ref. 11). Ether is highly flammable and therefore must be stored at controlled room temperature away from heat. Because exposure of ether to air causes rapid evaporation, the bottle should be tightly capped. Inhalation of ether vapors should be avoided due to undesirable hypnotic effects. Collodion vehicles are advantageous because they form an adherent, flexible, or rigid film which keeps the active ingredient at the site of action and prevents migration to surrounding tissue (Ref. 12). They also prevent moisture evaporation from the skin, thereby facilitating penetration of the active ingredient into the affected area resulting in sustained local action of the drug.

In a study by Strakosch (Ref. 3) on normal skin, the activity of salicyclic acid in several ointment base vehicles was compared. A direct relationship between the concentration of salicyclic acid and the time required to produce the same keratolytic action was observed. A salicyclic acid concentration of 1 percent produced keratolysis in 10 days, while a 3-percent concentration caused a keratolytic action equal to the 1-percent results in about 8 days. When the concentration was increased to 5 percent, keratolysis equal to the results obtained with both 1 and 3 percent occurred in 7 days. When the concentration was increased from 5 to 10 percent, the time to produce keratolysis was reduced to approximately 3 days. Test results indicated that increasing the concentration above 10 percent produced little difference in keratolytic effect. Both 10 and 15 percent concentrations gave very similar results. None of the studies, however, were done to correlate the concentration of salicyclic acid with its keratolytic activity on warts.

In a study by Bunney, Nolan, and Williams (Ref. 2) involving 95 patients, a wart paint consisting of 16.7 percent salicyclic acid and 16.7 percent lactic acid in flexible collodion gave a cure rate of 67 percent for common warts and 84 percent for plantar warts. The study noted that the paint was applied nightly by the patient at home, and results were assessed at the end of 12 weeks. Other wart paints tested in these trials that did not contain salicyclic acid were significantly less effective. The cure rates cited for the wart paint combination are comparable to those achieved under the supervision of a doctor with the use of liquid nitrogen which is considered by many dermatologists to be the treatment of choice in removing warts (Ref. 13).

A double-blind study by Arndt and Clark (Ref. 14) evaluated a combination of 16.7 percent salicyclic acid and 16.7 percent lactic acid in flexible collodion against a placebo over a 4-week study period, after application to multiple lesions on anatomically matched sites. There were 34 patients with multiple lesions included in the study, 25 with common warts, 5 with juvenile warts, 3

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statistical inferences. Also, the methods of assigning patients to a treatment group are unknown.

The prophylactic effect of various preparations of propionic acid was studied by Sulzberger and Kanof (Ref. *12*). For details, see part III. paragraph A.1.f. above—Undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate).

None of the above studies meet the effectiveness criteria set by the Panel. The Panel therefore concludes that at least one well-designed, controlled clinical trial is necessary to establish propionic acid and its salts (sodium propionate and zinc propionate) as effective in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Proposed dosage*—(i) *Concentration.* Sodium propionate, zinc propionate, and propionic acid may be used alone or in any combination to equal a total propionate concentration of 20.0 percent.

(ii) *Directions for use.* See part III. paragraph A.2. above—Category I Labeling.

(4) Labeling. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III. paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blinded, placebo-controlled clinical trial to determine the effectiveness of propionates in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

(*1*) Blacow, N., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, pp. 781–783, 1972.

(*2*) Heseltine, W. W., "A Note on Sodium Propionate," *Journal of Pharmacy and Pharmacology*, 4:120–122, 1952.

(*3*) Christensen, H. E., et al., "The Toxic Substances List," United States Department of Health, Education, and Welfare, Rockville, MD, pp. 785 and 793, 1973.

(*4*) Arena, J. M., "Poisoning," 3d Ed., Charles C. Thomas Publishing Co., Springfield, IL, p. 870, 1974.

(*5*) Goodman, L.S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 1010, 1975.

(*6*) OTC Volume 070032.

(*7*) Peck, S.M., et al., "Role of Sweat as a fungicide with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections," Archives of Dermatology and Syphilology, 39:126–148, 1939.

(*8*) Peck, S.M., E.F. Traub, and H.J. Spoor, "Aqueous Solutions of Sodium Propionate with Chlorophyll as a Therapeutic Agent," Archives of Dermatology and Syphilogy, 67:263–277, 1953.

(*9*) Keeney, E.L., et al., "Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and an In Vitro Comparison of Their Fungistatic and Antibacterial Effects with Other Ointments," Bulletin of the Johns Hopkins Hospital, 75:417–439, 1944.

(*10*) Keeney, E.L., and E.N. Broyles, "Sodium Propionate in the Treatment of Superficial Fungus Infections," Bulletin of the Johns Hopkins Hospital, 73:479–487, 1943.

(*11*) Sulzberger, M.B., H.C. Shaw, and A. Kanof, "Evaluation of Measures for Use Against Common Fungous Infections of the Skin. Screening Tests by Means of Paired Comparisons on Human Subjects," United States Naval Medical Bulletin, 45:237–248, 1945.

(*12*) Sulzberger, M.B., and A. Kanof, "Undecylenic and Propionic Acids in the Prevention and Treatment of Dermatophytosis," Archives of Dermatology and Syphilogy, 55:381–395, 1947.

p. *Salicylic acid.* The Panel concludes that salicylic acid is safe when used in a concentration less than or equal to 3 percent. But the Panel believes that there are insufficient data available to permit final classification of this ingredient for effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Salicylic acid is ortho-hydroxybenzoic acid and occurs as white crystals in fine needles or as a fluffy crystalline powder. It is slightly soluble in water, sparingly soluble in oils, fats, and waxes, and freely soluble in alcohols (Ref. *1*).

Salicylic acid was discovered in 1839 and was soon found to be the chief constituent of oil of wintergreen. Kolbe, a German organic chemist, developed a process for synthetically preparing salicylic acid from phenol. A modification of his method has been used since 1885 for commercial preparation (Ref. *2*).

The pharmacologic action of salicylic acid is diminished in the presence of alkaline substances because of the ionization of the acid (Ref. *2*).

(1) *Safety.* Preparations containing salicylic acid have been used topically for many years; however, salicylate toxicity and some deaths have been reported. A review of the literature revealed 13 deaths caused by the percutaneous absorption of salicylic acid. Ten of these deaths occurred in children. The diseases being treated included such varied conditions as psoriasis, scabies, dermatitis, and lupus vulgaris (Ref. *3*).

Salicylic acid applied to relatively small areas of skin or in concentrations less than 10 percent has been used without apparent ill effects as a kertolytic agent in the treatment of various skin disorders. In humans a blood level of from 30 to 50 mg of salicylic per 100 mL is generally considered to be toxic (Ref. *4*). The minimum intraperitoneal lethal dose in guinea pigs is 900 mg/kg. The minimum lethal dose orally in dogs is 450 to 550 mg/kg (Ref. *5*).

Kimura (Ref. *6*) reported that a 10-percent salicylic acid preparation in lanolin was applied for 3 hours to the legs of healthy male infants aged 3 to 16 months. Salicylate could be detected in the infants' urine 1 to 2½ hours after the drug was applied. The total amount of salicylic acid excreted in the urine varied between 0.55 and 3.0 mg, or between 0.06 and 0.3 percent of the total amount of drug applied. The surface area of application was 10 x 10 cm and was covered by a gauze pad.

Sautter, Buckwalter, and Ziffren (Ref. *4*) applied 40 percent salicylic acid in hydrophilic ointment to a surface burn covering 10 percent of a dog's body. The peak blood level of salicylic acid was 6.5 mg/100 mL with no toxic symptoms noted.

Forty percent salicylic acid ointment was applied to two human patients with burn surfaces no greater than 5 to 6 percent of the body. Serum salicylate levels were determined every 8 hours for 48 hours; the highest salicylate level reached was 15 mg/100 mL. No clinical symptoms of toxicity were observed (Ref. *4*).

Signs of toxicity were noted by von Weiss and Lever (Ref. *3*) after 3 to 6 percent salicylic acid ointment was applied to psoriatic lesions over a large part of the body six times a day. Serum levels of salicylic acid ranged from 48 to 64 mg/100 mL. Toxic effects were nausea, difficulty in breathing, impaired hearing, confusion, and hallucination. Most symptoms disappeared within 1 day after treatment stopped.

A more recent report described four patients with psoriasis on more than 25 percent of their bodies (Ref. *7*). A preparation containing 6 percent salicylic acid in a gel base was applied to the entire body surface below the neck immediately after showering. The treated areas were covered with a plastic wrap for 10 hours, after which the patients were allowed to shower again. This treatment was repeated daily for 5 days. Serum salicylate levels never exceeded 5 mg/100 mL in any of the patients, although more than 60 percent of the total applied salicylic acid was absorbed. No toxicity or accumulation of salicylic acid was observed.

Salicylic acid is a keratolytic agent. At concentrations higher than 3 percent it will destroy keratinized skin. Because of its keratolytic action, salicylic acid is known to be irritating to both the skin and the eyes. However, the concentration necessary to establish clinical signs of skin irritation depends on many factors, such as the vehicle, exposure time, and surface area occlusion. In higher concentrations, salicylic acid may delay wound healing, but this has not been fully assessed in the treatment of athlete's foot.

The systemic toxicity of topical salicylic acid, like its keratolytic effects, appears to result from a combination of factors. Some of these factors are (1) a high concentration of salicylic acid in a vehicle which allows rapid absorption, (2) the frequency of application, (3) whether the surface area is occluded, and (4) the condition and area of skin to which the preparation is applied (Ref. *7*).

It is recognized that absorbed salicylic acid is rapidly metabolized and excreted (Ref. *3, 4,* and *7*). Therefore, if the area of application is small, such as in athlete's foot or jock itch, systematic toxic concentrations of salicylic acid probably would not be reached. For example, if one assumes complete instantaneous absorption of the total dose of 1 g of a 3-percent salicylic acid preparation, the maximum amount in the blood at any one time would be 30 mg. This 30 mg of salicylic acid would be distributed into 7 L of blood, resulting in a maximum blood concentration of approximately 0.4 mg/100 mL. This is well below the 30- to 50-mg/100 mL level considered to be toxic.

Therefore, considering the worst case of absorption as described above, and the known rapid elimination of salicylic acid, the Panel considers the use of salicylic acid in topical preparations to be safe if the concentration is 3 percent or less, and if the use of this drug is restricted to relatively small body areas.

(2) *Effectiveness.* Salicylic acid is generally applied in ointment form and is used in dermatology for the following reasons: (1) to produce a keratolytic or macerating action; (2) as an antiseptic and antiparasitic; and (3) on the assumption that the addition of salicyclic acid to an ointment will promote the absorption of the other ingredients. Davies and Marks (Ref. *8*), using scanning electron microscopy of skin surface biopsies, suggested that the peeling effect of salicylic acid is due to the dissolution of intercellular cement material.

In vitro studies (Refs. *9* through *13*) have indicated that salicylic acid has some fungicidal activity. Dolan et al. (Ref. *14*) conducted a "semi-in vivo" study using epidermal scales of guinea pigs infected with *T. mentagrophytes.* Scales were placed in a stainless steel tissue capsule which was immersed in the test solution for 5, 15, 30, or 60 minutes. Then the scales were cultured on a Sabouraud's agar plate to see if the *T. mentogrophytes* were still living. The results were expressed as the time it took to kill the organism while in the presence of the antifungal ingredient. Salicylic acid was reported to have fungicidal activity with *T. mentagrophytes* cultured at 15 minutes, but not at 30 minutes.

The most extensive in vivo testing of salicyclic acid was done by Hopkins et al. (Ref. *15*). Over 7,500 patients at Fort Benning, Georgia, were treated for athlete's foot during a 3-year period. Cultures were obtained before treatment, but the cultured organisms were not identified. KOH preparations were examined at each visit. Although the total number of patients in the study was large, only 258 apparently received salicylic acid. Twenty-eight patients completed 4 weeks of treatment with salicylic acid: 47 percent were clinically clear at this time. The data were presented in an ambiguous fashion so that the actual success of salicylic acid is undeterminable.

Because of the lack of data on the effectivenes of topical salicylic acid for the treatment of athlete's foot, jock itch, and ringworm, the Panel recommends additional effectiveness testing.

(3) *Proposed dosage*—(i) *Concentration.* Salicylic acid 0.05 to 3.0 percent.

(ii) *Directions for use.* See part III. paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Cateogory I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part II. paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends one double-blind, placebo-controlled clinical trial to determine the effectivenss of salicyclic acid in the treatment of athlete's foot, jock itch, and ringworm. This study should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Cuidelines for Safety and Effectiveness Studies.)

References

(1) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 445–446, 1975.

(2) Osol, A., and G. E. Farrar, "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1207–1209, 1955.

(3) von Weiss, J. F., and W. F. Lever, "percutaneous Salicylic Acid Intoxicaton in Psoriasis," *Archives of Dermatolcgy,* 90:614–619, 1964.

(4) Sautter, R., J. A. Buckwalter, and S. E. Ziffren, "Chemicals and Enzymes in Debridement of Thermal Burns," *American Medical Association Archives of Surgery,* 76:744–748, 1958.

(5) OTC Volume 070045.

(6) Kimura, G., "Studies on Absorptive Function of the Skin and the Mucous Membrance of the Intestinal Canal of Infants in Respect to Salicylic Acid," *Oriental Journal of Diseases of Infants,* 28:13–14, 1940.

(7) Taylor, J. R., and K. Halprin, "Percutaneous Absorption of Salicylic Acid," *Archives of Dermatology,* 111:740–743, 1975.

(8) Davies, M., and R. Marks, "Studies on the Effect of Salicylic Acid on Normal Skin," *British Journal of Dermatology,* 95:187–192, 1976.

(9) Lyons, R. E., and C. S. Livingood, "Laboratory Test for the Evaluation of Fungicidal Solutions," *Archives of Dermatology and Syphilology,* 68:566–571, 1953.

(10) Scigliano, J. A., T. C. Grubb, and D. E. Shay, "Fungicidal Testing of Some Organo-Copper Compounds," *Journal of the American Pharmaceutical Association,* 39:673–676, 1950.

(11) Oster, K. A., and M. J. Golden, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. I. Evaluation of Fungistatic Laboratory Methods," *Journal of the American Pharmaceutical Association,* 36:283–288, 1947.

(12) Legge, L. T., L. Bonar, and H. J. Templeton, "Epidermomycosis at the University of California," *Archives of Dermatology and Syphilology,* 27:12–24, 1933.

(13) Emmons, C. W., "Fungicidal Action of Some Common Disinfectants on Two Dermatophytes," *Archives of Dermatology and Syphilology,* 28:15–21, 1933.

(14) Dolan, M. M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology,* 28:359–362, 1957.

(15) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology,* 7:239–253, 1946.

q. *Sulfur.* The Panel concludes that sulfur is safe but that there are insufficent data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Goodman and Gilman (Ref. *1*) summarize the history of sulfur as follows:

Sulfur has a long history in medicine. The practice of burning sulfur for the purification of the air is mentioned in the *Odyssey.* Hippocrates considered sulfur an effective antidote against plague. For the layman, sulfur has an undeserved reputation as an intestinal antiseptic, and the practice of an annual "spring cleansing" of the intestinal

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widely used on wounds, burns, and abrasions to treat or prevent surface infection. It has also been used as a scrub before and after surgery. Povidone-iodine contains about 10 percent available iodine.

Millikan (Ref. 1) evaluated the effectiveness of 7.5 percent povidone-iodine in two studies on acne patients. In the first study, providone-iodine was compared to its vehicle control in a double-blind fashion. Patients with mild acne washed two or three times daily with one of the treatments for 3 to 4 months. Evaluation was based on global impression. At the time of the study, 9 of the 10 patients using povidone-iodine were considered improved or much improved. In the control group, three out of seven patients were rated as improved.

Millikan (Ref. 1) also studied 27 patients with Grade II to IV acne (grading system based on type and location of lesions). Povidone-iodine was compared to the vehicle control, but in this study all patients also received systemic tetracycline concomitantly. There was no significant difference in effectiveness between the vehicle and providone-iodine. The author concluded that the oral tetracycline was responsible for this result.

Brown (Ref. 2) used a 7.5-percent povidone-iodine foam to treat 32 patients who had mild to moderate acne. The patients used the preparation twice daily for at least 6 months. Methods of evaluating patients were not defined. Of the 10 subjects using only povidone-iodine, 8 were good or fair at the conclusion of the trail. The remaining 22 patients used concomitant therapy including oral tetracycline, oral contraceptives, topical agents, and ultraviolet light. In this group, 19 patients showed a favorable response, but it is impossible to determine which ingredient produced this result.

In an uncontrolled study, Hudson (Ref. 3) evaluated the effectiveness of 7.5 percent povidone-iodine in 500 patients with moderate to severe acne. Patients washed with povidone-iodine one to three times daily for 3 months to more than 1 year. Tetracycline and sulfur lotions were used in addition to povidone-iodine. Hudson reported that the skin looked and felt less oily and that patient reaction was not defined and specific treatment results were not reported.

In an unpublished study (Ref. 4), 10 patients with Grade III acne (grading system was not defined) were treated twice daily with 7.5 percent povidone-iodine. A vehicle control was not used in this study. Patients were assessed by global impression 2 weeks after treatment and 4 weeks after treatment. All patients showed good or fair improvement. Lesion counts at the final visit compared to baseline showed decreases of 79 percent for pustules, 28 percent for open comedones, 18 percent for closed comedones, and 20 percent for papules.

The studies described above indicate that povidone-iodine may be an effective acne treatment; however, none of the studies met the Panel's effectiveness criteria. Deficiencies in study design included one or more of the following: (1) Lack of vehicle control, (2) concomitant therapy used, and (3) method of evaluating patients and treatment results not well defined. Also, none of the studies included a statistical analysis of results. Other studies were reviewed by the Panel (Ref. 4), but are not detailed here because they were not controlled and included concomitant therapy. The Panel concludes that povidone-iodine is of questionable effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration.* Povidone-iodine 7.5 percent.

(ii) *Directions for use.* See part III. paragraph A.2. above—Category I labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for products used in the treatment of acne. (See part III. paragraph A.2. above—Category I labeling.)

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

(5) *Evaluation.* The Panel recommends that studies be conducted to determine the stability of povidone-iodine and availability of elemental iodine from the complex. The Panel also recommends one double-blinded, vehicle-controlled clinical trial to determine the effectiveness of povidone-iodine in the treatment of acne. These studies should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

(1) Millikan, L. E., "A Double-Blind Study of Betadine Skin Cleanser in Acne Vulgaris," *CUTIS: Cutaneous Medicine for the Practitioner*, 17:394–396, 1976.

(2) Brown, F. J., "A Povidone-Iodine Skin Cleanser Foam in the Management of Acne Vulgaris," *British Journal of Clinical Practice*, 31:218–219, 1977.

(3) Hudson, A. L., "Betadine Skin Cleanser in Acne Vulgaris. Skin pH Determinations," *Clinical Trials Journal*, 10:23–25, 1973.

(4) OTC Volume 070239

Salicylic acid. The Panel concludes that salicylic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. Whatever the mode of administration, the toxic effects from overdosage are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and death. The possible toxic reactions are collectively known as salicylism.

The Panel reviewed the toxicity of salicylic acid in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Those data will not be repeated here. This discussion will include data dealing with salicylic acid in the treatment of acne or data received by the Panel since it completed its recommendations on topical antifungal drug products.

The major difference in the use of salicylic acid in acne as opposed to its use in fungal infections of the foot or groin is the very large surface area over which acne may be involved. In fact, roughly half of the body surface could be afflicted with acne. In adult humans, this would amount to close to 1 square meter of absorptive surface area.

Salicylic acid has been applied to relatively small areas of skin or in concentrations of less than 10 percent without apparent ill effects as a keratolytic agent in the treatment of various skin disorders. Salicylic acid for topical use on acne will be considered in concentrations ranging form 0.5 to 5 percent.

Most of the reports submitted for the use of salicylic acid in acne evaluated combination ingredient products. However, the following new data on salicylic acid as a single ingredient were contained in two submissions (Refs. 1 and 2). The acute oral LD_{50} of salicylic acid in male Sprague-Dawley rats was 800 mg/kg. When concentrations of 0.5 to 2 percent were applied to either normal or abraded skin of rabbits, salicylic acid was judged to be a mild irritant.

A lotion containing salicylic acid 2 percent was applied to normal and abraded rabbit skin at a rate of 2 mL/kg and held under occlusion for 24 hours (Ref. 3). If a rabbit weighed 2 kg, then it received 4 mL of the 2-percent lotion, amounting to a total of 80 mg salicylic

acid. There were no signs of acute toxicity in any of the test animals.

When an undiluted 2-percent salicylic acid lotion was applied to the eyes of rabbits and allowed to remain in the eye, the lotion was found to be an eye irritant. When the lotion was immediately washed out after application, there was no irritation (Ref. 3).

Five mL/kg of the lotion administered by oral gavage to female rats caused no toxic symptoms (total salicylic acid dose, 100 mg per 200 g rat). In mice the acute oral LD_{50} of the lotion was 32 mL/kg, or a total dose of approximately 666 mg/kg (Ref. 3).

In humans, a blood concentration of 30 to 50 mg salicylic acid per 100 mL is considered to be toxic (Ref. 4). If a human applied 15 g of a 5-percent salicylic acid preparation to the entire upper torso, the amount of salicylic acid available for absorption would be 750 mg. If all of this were instantly absorbed and distributed into 7 L of blood, the blood concentration would be approximately 10 mg/100 mL. Blood concentrations of 6.5 mg to 15 mg/100 mL have been reported to be nontoxic (Refs. 4 and 5). Based on this calculation and the data submitted, the Panel concludes that preparations containing up to 5 percent concentrations of salicylic acid would be safe for use in treating acne.

(2) *Effectiveness.* Salicylic acid has been used for over 100 years in the treatment of acne and various keratinizing diseases. It is used alone or often in combination with sulfur or resorcinol. Despite its long history of use, the exact mechanism of action has never been determined and, in fact, no study has documented the efficacy of salicylic acid used as a single ingredient in the therapy of acne.

An extensive review of the medicinal uses and pharmacologic properties of salicylic acid was published in a series of three articles coauthored by Weirich, Lauer, and Kirkwood (Refs. 6, 7, and 8). Weirich and his associates described specific pharmacological properties of salicylic acid and offered many reference sources to document their viewpoints. These properties included action such as germicidal, fungal protector, astringent, antipruritic, and anti-inflammatory. Other properties discussed were a deep keratolytic action at concentrations greater than 5 percent, superficial surface keratolytic action up to 4 percent, and an acidifying effect at 1 percent and above. The ability to produce an increase in penetration of topical drugs was also described. It is unknown which, if any, of these actions is responsible for the clinical responses noted in acne. It is usually assumed, however, that salicylic acid is working as a keratolytic agent and possibly as a substance which promotes the penetration of other active ingredients. Shalita (Ref. 9), Leyden (Ref. 10), and Plewig and Kligman (Ref. 11) believe that salicylic acid, in addition to its keratolytic and anti-inflammatory action, has a comedolytic effect; that is, it causes an increased turnover of follicular ephithelial cells and an apparent decrease in the cohesiveness of these cells when they are shed into the cavity of the follicle.

A commercial product containing 2 percent sulfur and 2 percent salicylic acid in a cream base has been studied in numerous investigations (Refs. 12, 13, and 14). One study was conducted to show the effectiveness of this preparation in seborrhea associated with acne. Robinson (Ref. 12) treated 120 patients using either a cake or cream containing 2 percent sulfur and 2 percent salicylic acid. Although the specific details of the study were not given, the investigator noted, "* * * (the) cake and cream quickly dried the skin and were particularly helpful in cleansing comedones."

In another study, Riley (Ref. 13) treated 150 acne patients with a salicylic acid-sulfur combination. Depending upon the severity of the acne condition, the treatment also included a restricted diet, ultraviolet light, acne surgery, astringents, colloidal sulfur, oral vitamin A, oral antibiotics, or X-ray therapy. All patients were instructed to wash their faces with ordinary soap for the first 2 weeks. At the end of the 2-week preliminary phase, patients showing little improvement were continued on the same therapeutic routine except for washing with a 2-percent salicylic acid-2 percent sulfur cream or cake instead of soap. The patients used the salicylic acid-sulfur combination one to four times daily for 4 to 12 months. The method of evaluating patients was not explained. Results showed a good response in 147 patients. The salicylic acid-sulfur combination was helpful in one patient, but two others had a poor response. Riley concluded that the cream or cake containing salicylic acid and sulfur did contribute to the improvement of acne vulgaris. However, the study made no mention of blinding or randomization, and the results were not evaluated statistically.

Baird (Ref. 14) treated 371 patients with acne vulgaris, with 133 cases classified as severe and 238 as moderate. All patients followed a simple, restricted diet, washed their faces with the 2-percent salicylic acid-2 percent sulfur cream, and were treated with acne surgery. In addition, the severe cases may have been treated with X-rays, oral antibiotics, staphylococcus vaccines, or estrogenic hormones. In conclusion, the investigator stated that the simplified treatment plan improved all the mild to moderate cases of acne. In the severe cases, the author believed that scrubbing with the cream shortened the course of therapy. However, the study made no mention of vehicle control, blinding, randomization, or statistical analysis.

In another study, using a randomized but not blinded method, 109 patients were treated once or twice daily with a 2-percent salicylic acid lotion or a commercially available soap (Ref. 3). Patients included in the study had mild to moderate acne. They were evaluated by global assessment after 4, 7, and 14 days. After 14 days the lotion proved to be significantly superior to the soap for reducing blackheads ($p = 0.029$). There were no statistically significant differences between the two products in the frequency of "breaking out" in acne blemishes, in improvement in overall condition, or in reduction of blemishes (inflammatory lesions). The researchers considered 14 days inadequate to evaluate the frequency of "breaking out." Consequently, a somewhat similar study of 117 patients with mild to very severe acne was conducted for 3 months. The study was blinded.

In this 3-month study, patients were untreated for 2 weeks before enrollment in the study (Ref. 3). After evaluation, they were randomly assigned to the 2-percent salicylic acid lotion (57 patients) or the commercially available soap (60 patients). Patients were treated once or twice daily depending upon the severity of their acne and the oiliness of their skin. The severity of blackheads, pimples, and oiliness was measured as 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. The overall clinical evaluation showed good to excellent results in 72.2 percent of the patients treated with salicylic acid compared with 10.5 percent of those who had used the soap. The group using the salicylic acid lotion had a statistically significant greater improvement than the group using the soap ($p < 0.001$). More importantly, fewer blackheads and pimples were observed in the lotion-treated group. The average reduction in "severity units" at 3 months compared with baseline for salicylic acid was 1.28 for blackheads and 1.41 for pimples. For soap the average reduction was 0.37 for blackheads and 0.19 for pimples. These results were statistically significant at

Final Rule: Labeling for Oral and Rectal OTC Aspirin and Aspirin-Containing Drug Products: Reye Syndrome Warning

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June 9, 1988

21 CFR Part 201

[Docket No. 87N-0371]

Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Drug Products; Reye Syndrome Warning

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is making permanent the regulation that requires a Reye syndrome warning on the labeling of oral and rectal over-the-counter (OTC) human drug products containing aspirin. The current regulation expires on June 8, 1988, unless extended by FDA. In addition, the agency is revising the warning statement to state clearly that Reye syndrome is reported to be associated with aspirin. These actions are based primarily on the results of a study by the Public Health Service (PHS) Reye Syndrome Task Force and the report of the Institute of Medicine's Committee on Reye Syndrome and Medication Use. The PHS study confirms earlier reports of an association between Reye syndrome and aspirin use in children and teenagers with chicken pox or flu.

EFFECTIVE DATES: Continuation of the current warning statement effective June 9, 1988; revision of the warning statement effective December 9, 1988.

FOR FURTHER INFORMATION CONTACT: Howard P. Muller, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of March 7, 1986 (51 FR 8180), FDA published a final regulation requiring the following labeling statement on oral and rectal OTC drug products containing aspirin: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness." FDA took this action to aid in increasing the public's awareness of the association between the use of aspirin and Reye syndrome [1] and to bring uniformity and consistency to the labeling of aspirin and aspirin-containing drug products in the marketplace. The 1986 regulation was based, in large part, on the results of a "pilot study" conducted by PHS which showed an association between the use of aspirin and the onset of Reye syndrome.

The 1986 final rule also provided that the regulation would expire June 8, 1988, 2 years from the effective date, unless the agency acted to extend it. This 2-year period was to allow for the completion and evaluation of further research by PHS, known as the "main study," into the association between Reye syndrome and various exposure factors, including the use of aspirin.

1. The PHS Main Study.

The PHS main study confirmed the results of the pilot study and found a large, statistically significant association between Reye syndrome in children and teenagers and the ingestion of aspirin during previous illnesses. The PHS report, entitled "Reye Syndrome and Medications—Report of the Main Study," November 12, 1986, was prepared by the PHS Reye Syndrome Task Force (Ref. 1). The PHS report was evaluated by the Institute of Medicine (IOM) of the National Academy of Sciences in a report entitled "The PHS Study of the Reye Syndrome: Review of a Continuing Study—Report Number 6—Review of the PHS Continuing Study by the Committee on the Reye Syndrome and Medications," February 1987 (Ref. 2). A report of the main PHS study was published in the *Journal of the American Medical Association* on April 10, 1987 (Ref. 3). These reports have been placed on display with the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, under Docket No. 87N-0371. Additional background information may be found in Docket Nos. 82N-0158 and 85N-0553.

The PHS main study concluded that the association between Reye syndrome and aspirin is consistent with estimates of risk determined in earlier studies and reflects the strength of the epidemiologic association observed in those studies. The study reinforced the importance of reducing the use of aspirin in the treatment of children and teenagers with chicken pox and flu-like illnesses. FDA believes that the available evidence supports the continuing need to maintain a high level of public awareness of the association between the use of aspirin in children and teenagers with chicken pox and flu and the incidence of Reye syndrome.[2] Accordingly, based on the results of this PHS research, in the Federal Register of January 22, 1988 (53 FR 1796), FDA published a proposed rule to make permanent the requirement regarding the Reye syndrome warning.

2. Public Education Program

In its efforts to create and maintain a high level of public awareness of the association between the use of aspirin in children and teenagers and the incidence of Reye syndrome, FDA has conducted an extensive public education program in addition to the required warning information on aspirin product labeling. FDA has initiated public educational activities on Reye syndrome for several years, beginning in 1982. Earlier educational efforts were directed at raising the awareness of Reye syndrome among parents of young children. More recently, FDA has focused its educational program towards teenagers who may still be unaware of the association between Reye syndrome and aspirin use for their age group during the flu or chicken pox. Accordingly, during 1987, the agency distributed approximately 40,000 posters to high schools and colleges warning of the association between Reye syndrome and the ingestion of aspirin during illness with the flu or chicken pox. In addition, FDA distributed public service announcements to approximately 2,000 radio stations, and sent advertisements to approximately 11,000 daily and weekly newspapers across the United States, with the message consistently directed toward teenagers.

The aspirin industry, through the Aspirin Foundation of America, has also conducted an extensive public education program during the past several years. Public service announcements were distributed to television and radio stations around the

[1] Reye syndrome is a rare but serious illness affecting children and teenagers. Characteristically, its onset follows illness due to influenza B, influenza A, or chicken pox as the child or teenager appears to be getting well. Reye syndrome is a degenerative disease of the brain; the symptoms include nausea, vomiting, and behavioral changes.

[2] The preliminary results of another Reye syndrome study, conducted by Yale University, have been presented to FDA. These results support the conclusion of the PHS study. The final report from the Yale study is expected within the next several months.

country, as well as the major networks, beginning in the spring of 1985 and continuing in each of the succeeding three flu seasons. As with the FDA efforts, recent educational initiatives have sought to reach teenage audiences, by featuring teenage television and radio personalities in public service announcements. Several retail grocery and pharmacy stores and chains have also participated in a number of educational efforts regarding Reye syndrome.

3. Decline in Incidence of Reye Syndrome

The Centers for Disease Control has reported that the number of cases of Reye syndrome has declined significantly between 1980 (658 cases) and 1985 (93 cases). Moreover, according to a study published in *Pediatrics* in June 1987 ("National Patterns of Aspirin Use and Reye Syndrome Reporting, United States, 1980 to 1985") (Ref. 4), pediatric aspirin use during that same time also declined. These favorable trends appear to be continuing, with 101 Reye syndrome cases reported for 1986 in the *Morbidity and Mortality Weekly Report* (Ref. 5). Although the data show a decline in Reye syndrome cases over the past few years, the fact that 101 cases were reported as recently as 1986 indicates the continuing need for a clear and uniform Reye syndrome warning on aspirin-containing drug products and for a continued public education program.

II. Highlights of the Final Rule

As described further below, all the comments received on the proposed rule expressed support for continuing the Reye syndrome warning requirement. The final rule, therefore, makes permanent the requirement that all orally and rectally administered OTC aspirin products bear an appropriate Reye syndrome warning.

The final regulation revises the warning statement to make clear that aspirin use in children and teenagers has been reported to be associated with Reye syndrome. Specifically, the final regulation amends the previous warning by adding the phrase "reported to be associated with aspirin" at the end, so that the new Reye syndrome warning reads as follows: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness *reported to be associated with aspirin*." FDA believes the revision is appropriate and necessary to reflect the PHS study finding of a large, statistically significant association between Reye syndrome and the ingestion of aspirin during chicken pox or flu. As with the 1986 regulation, this revised warning, once fully implemented, will provide consumers with a clear and consistent message and will continue to ensure consistency and uniformity in the marketplace.

The final rule also continues the requirement in the 1986 regulation that the Reye syndrome warning be "prominent." Such prominence is achieved, in part, by the regulation's continuing requirement that the Reye syndrome warning be the first warning on the label under the "WARNINGS" heading. In addition, in order to call consumers' attention to the revised wording of the Reye syndrome warning, FDA is interpreting the requirement for prominence as requiring, for a period of 1 year, an attention-getting statement on the principal display panel of the product.

Finally, the revised warning is required to appear on affected product packages that are initially introduced or initially delivered for introduction into interstate commerce by December 9, 1988. Until the effective date of the revised Reye syndrome warning, the current Reye syndrome warning requirement remains in effect.

III. Comments

The proposal provided 60 days for public comment. FDA received 17 comments on the proposed rule. The comments were submitted by drug companies, pharmaceutical trade associations, consumer groups, professional medical associations, congressional representatives, individual health practitioners, and groups representing the interests of victims of Reye syndrome. All comments generally supported a continued requirement for a Reye syndrome warning. A summary of the comments received by FDA during the comment period and the agency's response to them follows:

1. Text of Warning Statement

Several comments expressed concern about the precise language of the warning statement. The major concern raised was that the warning should be revised to make clear the concept of an association between Reye syndrome and aspirin use. One comment also recommended that the warning's reference to "chicken pox or flu symptoms" be removed, contending that reports of Reye syndrome associated with aspirin use have not been limited to patients suffering from varicella or influenza. Another comment urged that the warning note the potential fatal consequences of Reye syndrome. This comment argued that individuals do not always appreciate the seriousness of a warning unless it discloses the consequences that can result if the warning is not heeded.

FDA agrees with the suggestion that the warning statement should be revised to make clear that aspirin use in children has been reported to be associated with Reye syndrome. Now that the PHS study has been completed and has reported a large, statistically significant association between Reye syndrome and aspirin use, FDA believes it is appropriate and necessary that the warning statement indicate this association. Accordingly, the warning statement has been revised to read: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin."

FDA does not believe that the other issues raised by the comments warrant changes in the final rule. FDA believes it appropriate at this time that the warning continue to refer to "chicken pox and flu symptoms" because these symptoms were the symptoms of most of the antecedent illnesses in the PHS study on which FDA is relying as the scientific justification for the warning requirement. In addition, FDA believes that the warning's reference to Reye syndrome as a "serious illness" is sufficient for consumers to appreciate the medical importance of the warning statement. Accordingly, based on the data available at this time, FDA does not believe that further changes to the warning statement in the final rule are now necessary.

2. Prominence of Required Warning

Several comments suggested that the required Reye syndrome warning be given more prominence on aspirin drug product labeling. Comments variously urged that the warning statement be made conspicuous through large type size or be set off by use of a contrasting color. One comment recommended that the entire warning statement be boxed.

FDA agrees that it is essential to bring the Reye syndrome warning to the attention of the consumer. In order to achieve this, the final rule continues the requirement in the current regulation that the Reye syndrome warning appear "prominently" on the label. This includes the requirements that the Reye syndrome warning appear as the first warning on all labeling of aspirin drug products under the heading "Warnings" that the warning must appear on the

immediate container label and on the retail package; and that the warning must appear on all product labeling that contains warnings. These provisions thus help assure that the warning statement will be seen and read by the consumer.

In addition, because the text of the Reye syndrome warning is being revised, FDA interprets the "prominence" requirement in the regulations (21 CFR 201.15 and 201.315(h)(1)), in the unique circumstances presented here, as requiring that the principal display panel call consumers' attention to the new warning. Specifically, FDA interprets this as requiring manufacturers of aspirin and aspirin-containing drug products to provide an attention-getting statement, such as a "flag," alerting consumers to the revised Reye syndrome warning. A phrase using the words "new" and "warning," such as one of the following phrases, should be used: (1) "See new warning for children/teens"; (2) "Read new label warning"; or (3) "Read new warning for children/teens." To assure that consumers are alerted to the new warning, the language of the attention-getting statement must: (i) Appear on the principal display panel; (ii) be carried in type size which is conspicuous; and (iii) be carried for 1 year after the revised Reye syndrome warning statement is added to the labeling. For that 1-year period, FDA will view as misbranded any aspirin or aspirin-containing OTC drug product whose principal display panel fails to contain an appropriate attention-getting statement.

FDA is not prescribing a minimum type size or use of contrasting color for the warning. However, under section 502(c) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(c)), a drug is misbranded if a required labeling statement is not sufficiently prominent to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use. Agency regulations state that a labeling statement may lack the prominence and conspicuousness required by section 502(c) of the act by reason, among others, of "[s]mallness or style of type in which such * * * statement * * * appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter." (21 CFR 201.15(a)(6).) In its surveillance of OTC drug products FDA routinely examines the warning statements on aspirin products to be sure that these requirements regarding prominence and conspicuousness of the warning statements have been met.

3. Australian Study

One comment said the proposed warning statement is acceptable as currently worded and advised against changing the language to make it more stringent. The comment was reacting to a letter referenced in the proposal which advocated a stronger warning statement. The comment contended that the association between Reye syndrome and aspirin is not supported by all studies. Specifically, the comment referred to an Australian study that found no correlation between the use of aspirin and the occurrence of Reye syndrome. The comment concluded that the current warning statement is sufficient in light of the lack of complete agreement among the studies.

FDA does not find the results of the Australian study cited by the comment to be persuasive. The Australian study, reported in *Pediatrics* (Ref. 6), is a retrospective review of medical records of patients hospitalized during a 10-year period between 1973 and 1982. Unlike the PHS study, the Australian study was not controlled. Moreover, medication histories for the period before hospitalization were based on chart reviews, a less reliable method of gathering data than that followed in the PHS study. The reported cases in the Australian study were predominantly in a very young age group, in which metabolic errors may be indistinguishable from Reye syndrome. Therefore, the identification of cases as Reye syndrome cases in the Australian study is questionable. The approach of applying new criteria to a review of older medical records is certainly not as reliable as the rigorous approach prospectively developed and applied in the PHS studies. The agency continues to believe that the evidence from research to date clearly indicates a strong association between Reye syndrome and the ingestion of aspirin.

4. Adult-only Aspirin

One comment suggested that FDA permit labeling for aspirin-containing drug products that are not intended for use by children or teenagers to bear this special warning statement: "Warning: This medicine is not for children or teenagers. Children and teenagers should not use this medicine because of concerns about Reye Syndrome, a rare but serious illness."

FDA does not agree with this suggestion. As stated more fully in the proposal of December 17, 1985 (50 FR 51400), FDA believes that the public interest is best served by assuring that the same warning statement is used on all products covered by the regulation. This approach eliminates the potential for consumers being confused by various forms of the warning statement.

5. Other Salicylates

Another comment recommended that the labeling warning statement be required not only for aspirin and aspirin-containing drug products, but for all products containing salicylates.

FDA notes that the scientific research to date, on which the Reye syndrome warning statement requirement is based, focuses on the association between Reye syndrome and aspirin, rather than on the broader category of drug products containing nonaspirin salicylates. Indeed, the PHS study reported that there were too few subjects with reported exposures to nonaspirin salicylates for a meaningful analysis. FDA believes at the present time that priority must be given to continuing the warning on aspirin and aspirin-containing products. FDA will consider extending the scope of the warning requirement to nonaspirin salicylates at some time in the future, if warranted by further research or other appropriate information.

6. Changing the Marketing Status of Certain Aspirin Products

Several comments suggested that FDA require that aspirin be removed as an ingredient from compounds that may be used by individuals under 21 years of age. Another comment proposed that aspirin be available for children and adolescents only under a physician's prescription.

FDA believes that continuing to require a Reye syndrome warning statement on aspirin and aspirin-containing OTC drug products is sufficient and that the more drastic measures of banning use of aspirin in products for individuals under 21 years of age or limiting such products to prescription use are unnecessary. As noted, the latest epidemiological data indicate a marked decline in the incidence of Reye syndrome among children and adolescents since 1980. FDA does not believe that removing aspirin from compounds used by individuals under 21 years of age would be justifiable because other aspirin-containing compounds would still be readily available for administration to children and teenagers. Moreover, the agency believes that OTC aspirin-containing products properly labeled with the Reye syndrome warning statement can be safely used in the proper circumstances by individuals

under 21 years of age. Therefore, FDA disagrees with the suggestion that aspirin for individuals under 21 years of age be made available only under a physician's prescription.

7. Labeling in Spanish

Two comments suggested that the current warning statement would be more effective if it were also required to be in Spanish.

Under FDA labeling regulations (21 CFR 201.15(c)), labeling may be written in the predominant local language when it is distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English. Although in the 50 states all required labeling must appear in English, the regulations do not preclude the distribution of labeling in a language other than English, in a special format, or in Braille along with the conventional English language labeling. FDA encourages the preparation of labeling to meet the needs of non-English speaking or special user populations so long as such labeling fully complies with agency regulations.

Effective Dates

The agency believes it is of the utmost importance that there be no time gap in the requirement for a Reye syndrome warning statement on aspirin and aspirin-containing drug products. The available evidence supports the continuing need to maintain a high level of public awareness of the risks of use of aspirin in children and teenagers. In addition, no additional costs associated with labeling changes would result from this action, since it would simply require the continued use of labeling already prepared. Because of the importance to the public health of assuring that the labeling of all oral and rectal OTC aspirin products bears a Reye syndrome warning, the Commissioner finds good cause for making effective immediately that part of this final rule which makes a Reye syndrome warning statement a permanent requirement. Accordingly, § 201.314 is revised by deleting paragraph (h)(5) effective June 9, 1988.

This final rule also amends the warning statement to read: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin." To provide aspirin drug product manufacturers with adequate lead time to make the necessary printing changes, this provision is effective December 9, 1988. After December 9, any orally or rectally administered aspirin or aspirin-containing product that does not contain the revised warning statement and that is initially introduced or initially delivered for introduction into interstate commerce is misbranded under sections 201(n) and 502 (a) and (f) of the act (21 U.S.C. 321(n) and 352 (a) and (f)). As noted earlier, until the effective date of the revised Reye syndrome warning, the current Reye syndrome warning requirement remains in effect.

Also as noted in the response to comment number 2 above, after December 9, 1988, FDA will view as misbranded under section 502 of the act any aspirin drug product subject to this regulation that is initially introduced or initially delivered for introduction into interstate commerce and that does not contain an appropriate attention-getting statement on the principal display panel. To assure that consumers are alerted to the new warning statement for at least the equivalent of a single flu season, the attention-getting statement is to be carried on the principal display panel of each product subject to this regulation that is initially introduced or initially delivered for introduction into interstate commerce until December 11, 1989.

FDA believes that a 6-month effective date for the revised warning statement gives manufacturers sufficient time to make the required labeling changes. FDA recognizes, however, that there may be a few small manufacturers for whom, for various financial or other reasons, it is impossible to comply with the revised labeling provision of this final rule by the effective date. In these unusual circumstances, FDA will consider requests for limited extensions. Such requests should be sent to Office of Compliance, Center for Drug Evaluation and Research (HFD-300), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, and should document both the need for a extension and the duration of time requested.

III. Economic Impact

FDA has examined the regulatory impact and regulatory flexibility implications of the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act. This regulation requires manufacturers to incur costs for making one-time typesetting changes to the Reye syndrome warning statement in the product label. The warning statement appears on the immediate container label and, in those cases where the immediate container is not the retail package, also on the retail package label. In addition, the warning statement must appear on any labeling that contains warnings. Therefore, this action may require one-time typesetting changes for as many as three labels per product.

In addition, this regulation requires manufacturers to incur costs for making one-time typesetting changes to the principal display panel on a product's label to include an attention-getting statement or flag bringing to the consumer's attention the warning statement.

Any costs incurred by manufacturers as a result of discarding outdated label inventories would be negligible because the regulation gives 6 months of update labels before products are initially introduced or initially delivered for introduction into interstate commerce.

FDA estimates that the regulation will impose direct one-time costs associated with changing product labels that total less than $6 million. Therefore, the agency has determined that the final rule is not a major rule as defined in Executive Order 12291. Further, FDA certifies that the final rule will not have a significant impact on a substantial number of small entities as defined by the Regulatory Flexibility Act.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. References

The following information has been placed in the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

(1) "Reye Syndrome and Medications—Report of the Main Study," Public Health Service Reye Syndrome Task Force, November 12, 1986.

(2) "The PHS Study of the Reye Syndrome: Review of a Continuing Study—Report Number 6—Review of the PHS Continuing Study by the Committee on the Reye Syndrome and Medications," Institute of Medicine of the National Academy of Sciences, February 1987.

(3) Hurwitz, E.S., et al., "Public Health Service Study of Reye's Syndrome and Medications, Report of the Main Study," *Journal of the American Medical Association*, 257(14): 1905-1911, 1987.

(4) Arrowsmith, J.B., et al., "National Patterns of Aspirin Use and Reye Syndrome Reporting, United States, 1980 to 1985," *Pediatrics*, 79:858-863, June 1987.

(5) *Morbidity and Mortality Weekly Report*. Vol. 36. No. 41. October 23. 1987.
(6) Orlowski. James P., et al., "A Catch in the Reye," *Pediatrics*. 80:638–642. November 1987. C0001. Docket No. 87N–0371. Dockets Management Branch.

List of Subjects in 21 CFR Part 201

Drug. Labeling.

Therefore. under the Federal Food. Drug. and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs. Part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR Part 201 continues to read as follows:

Authority: Secs. 501. 502. 701. 52 Stat. 1049–1051 as amended. 1055–1056 as amended (2 U.S.C. 351. 352. 371); 21 CFR 5.10; § 201.21 also issued under secs. 301. 505. 52 Stat. 1042–1043 as amended. 1052–1053 as amended (21 U.S.C. 331. 355).

2. Section 201.314 is amended by revising the warning statement in paragraph (h)(1) and by removing (h)(5) to read as follows:

§ 201.314 Labeling of drug preparations containing salicylates.

* * * * *

(h)(1) * * * "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome. a rare but serious illness reported to be associated with aspirin."

* * * * *

Dated: May 25. 1988.

Frank E. Young.

Commissioner of Food and Drugs.

[FR Doc. 88–13058 Filed 6–7–88. 11:35 am]

BILLING CODE 4160–01–M

FINAL REPORT

Safety Assessment of Salicylic Acid, Butyloctyl Salicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate

September 12, 2000

The 2000 CIR Expert Panel Members: Chairman Wilma Bergfeld, M.D., F.A.C.P., Donald Belsito, M.D., Paul W. Snyder, Ph.D., D.V.M., Curtis Klaassen, Ph.D., Arnold. L. Schroeter, M.D., and Ronald C. Shank, Ph.D., and Thomas Slaga, Ph.D. CIR Director: F. Alan Andersen, Ph.D.

Cosmetic Ingredient Review

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FINAL REPORT

Safety Assessment of Salicylic Acid, Butyloctyl Salicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate

ABSTRACT

Salicylic Acid is an aromatic acid used in cosmetic formulations as a denaturant, a hair conditioning agent, and a skin conditioning agent - miscellaneous in a wide range of cosmetic products at concentrations ranging from 0.0008% to 3%. The Calcium, Magnesium, and MEA salts are preservatives, and Potassium Salicylate is a cosmetic biocide and preservative, not currently in use. Sodium Salicylate is used as a denaturant and preservative (0.09% to 2%). The TEA salt of Salicylic Acid is used as a UV light absorber (0.0001% to 0.75%). Several Salicylic Acid esters are used as skin conditioning agents - miscellaneous (Capryloyl, 0.1% to 1%; C12-15 Alkyl, no current use; Isocetyl, 3% to 5%; Isodecyl, no current use; and Tridecyl, no current use). Butyloctyl Salicylate (0.5% to 5%) and Hexyldodecyl Salicylate (no current use) are hair conditioning agents and skin conditioning agents - miscellaneous. Ethylhexyl Salicylate (formerly known as Octyl Salicylate) is used as a fragrance ingredient, sunscreen agent, and UV light absorber (0.001% to 8%), and Methyl Salicylate is used as a denaturant and flavoring agent (0.0001% to 0.6%). Myristyl Salicylate has no reported function. Isodecyl Salicylate is used in 3 formulations, but no concentration of use information was reported. Salicylates are absorbed percutaneously, with more glucuronides and more unmetabolized Salicylic Acid than when absorbed from the stomach. Around 10% of applied salicylates can remain in the skin. Salicylic Acid is reported to enhance percutaneous penetration of some agents (e.g. vitamin A), but not others (e.g., hydrocortisone). Little acute toxicity (LD_{50} in rats; >2 g/kg) via a dermal exposure route is seen for Salicylic Acid, Methyl Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. Short-term oral, inhalation, and parenteral exposures to salicylates sufficient to produce high blood concentrations are

associated primarily with liver and kidney damage. Subchronic dermal exposures to undiluted Methyl Salicylate were associated with kidney damage. Chronic oral exposure to Methyl Salicylate produced bone lesions as a function of the level of exposure in 2 yr rat studies; liver damage was seen in dogs exposed to 0.15 g/kg/d in one study; kidney and liver weight increases in another study at the same exposure; but no liver or kidney abnormalities in a study at 0.167 g/kg/d. Application of Isodecyl, Tridecyl, and Butyloctyl Salicylate were not irritating to rabbit skin, while undiluted Ethylhexyl Salicylate produced minimal to mild irritation. Methyl Salicylate at concentrations >50% and a 1% concentration with a 70% ethanol vehicle were irritating, while a 6% concentration in polyethylene glycol produced little or no irritation. Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate were not ocular irritatants. While Salicylic Acid at a concentration of 20% in acetone was positive in the local lymph node assay, a concentration of 20% in acetone/olive oil was not. Methyl Salicylate was negative at concentrations up to 25% in this assay, independent of vehicle. Maximization tests of Methyl Salicylate, Ethylhexyl Salicylate, and Butyloctyl Salicylate produced no sensitization in guinea pigs. Neither Salicylic Acid nor Tridecyl Salicylate were photosensitizers. Salicylic Acid, produced when aspirin is rapidly hydrolyzed to Salicylic Acid after absorption from the gut, was reported to be the causative agent in aspirin teratogenesis in animals. Dermal exposures to Methyl Salicylate, oral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate, and parenteral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate are all associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure. An exposure assessment of a representative cosmetic product used on a daily basis is available which estimates that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. Studies of the genotoxic potential of Salicylic Acid, Sodium Salicylate, Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate were generally negative. Methyl Salicylate, in a mouse skin painting study, did not induce neoplasms. Likewise, Methyl Salicylate was negative in a mouse pulmonary tumor system. Salicylic Acid (2%) produced minimal cumulative irritation and slight or no irritation(1.5%); TEA-Salicylate (8%) produced no irritation; Methyl Salicylate (>12%) produced pain and erythema, a 1% aerosol produced erythema, but an 8% solution was not irritating; Ethylhexyl Salicylate (4%) and undiluted Tridecyl Salicylate produced no irritation. In atopic patients, Methyl Salicylate caused irritation as a function of concentration (no irritation at concentrations of 15% or less). In normal skin, Salicylic Acid, Methyl Salicylate, and Ethylhexyl (Octyl) Salicylate are not sensitizers. Salicylic Acid is not a photosensitizer, nor is it phototoxic. Salicylic Acid and Ethylhexyl Salicylate are low-level photoprotective agents. Salicylic Acid is well-documented to have keratolytic action on normal human skin. Because of the possible use of these ingredients as exfoliating agents, a concern exists that repeated use may effectively increase exposure of the dermis and epidermis to ultraviolet radiation, an effect opposite the known ultraviolet radiation absorption Data were not available that suggest what the balance of these two influences would be, so it was concluded that the prudent course of action would be to advise the cosmetics industry that there is a risk of increased ultraviolet radiation damage with the use of any exfoliant, including Salicylic Acid and the listed salicylates, and that steps need to be taken to formulate cosmetic products with these ingredients as exfoliating agents so as not to increase sun sensitivity, or when increased sun sensitivity would be expected, to include directions for the daily use of sun protection. The available data were not sufficient to establish a limit on concentration of these ingredients, or to identify the minimum pH of formulations containing these ingredients, such that no skin irritation would occur, but it was recognized that it is possible to formulate cosmetic products in a way such that significant irritation would not be likely, and it was concluded that the cosmetics industry should formulate products containing these ingredients so as to be non irritating. While simultaneous use of several products containing Salicylic Acid could produce exposures greater than would be seen with use of baby aspirin (an exposure generally considered to not present a reproductive or developmental toxicity risk), it was not considered likely that consumers would simultaneously use multiple cosmetic products containing Salicylic Acid. Based on the available information, the CIR Expert Panel reached the tentative conclusion that these ingredients are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection are provided.

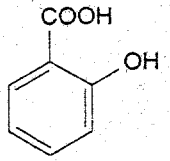
INTRODUCTION

This report reviews the safety of Salicylic Acid; its Calcium, Magnesium, MEA, Potassium, Sodium, and TEA salts; its acid ester, Capryloyl Salicylic Acid; and its Butyloctyl, C12-15 Alkyl, Ethylhexyl, Isocetyl, Hexyldodecyl, Isodecyl, Methyl, Myristyl, and Tridecyl alcohol esters. This family of ingredients was determined based on similarity of structure and/or function in cosmetics. Ethylhexyl Salicylate was formerly known as Octyl Salicylate. Amyl Salicylate, while structurally similar to the other salicylate esters (see next section), was not included because its only listed function (Wenninger et al., 2000) is as a fragrance ingredient, which excludes it from review according to CIR procedures.

CHEMISTRY

DEFINITION AND STRUCTURE

Salicylic Acid (CAS No. 69-72-7) is the aromatic acid that conforms to the formula (Wenninger et al., 2000):

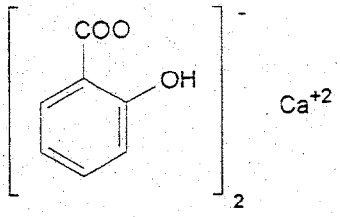


It is also known as 2-Hydroxybenzoic Acid (Wenninger et al., 2000; Lide, 1993; Lewis, 1993a; Budavari, 1989); Benzoic Acid, 2-Hydroxy (Wenninger et al., 2000; Gennaro, 1990); o-Hydroxybenzoic Acid (Wenninger et al., 2000; Lewis, 1993a; 1993b; Gennaro, 1990); o-Hydroxy Benzoic Acid (Sax, 1979); and Orthohydroxybenzoic Acid (Lewis, 1993a).

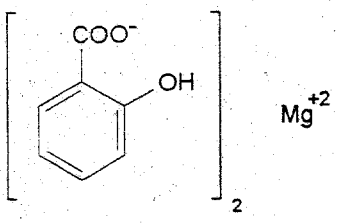
Salicylic Acid Salts

Calcium Salicylate (CAS No. 824-35-1) is the calcium salt of Salicylic Acid (q.v.) that is also known as Salicylic Acid, Calcium Salt; Calcium 2-Hydroxybenzoate; and Benzoic Acid, 2-Hydroxy-, Calcium Salt (Wenninger et al., 2000).

It conforms to the formula (Wenninger et al., 2000):

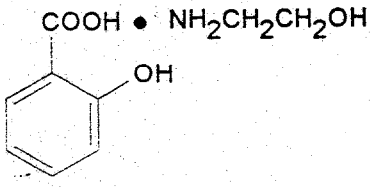


Magnesium Salicylate (CAS No. 18917-89-0) is the magnesium salt of Salicylic Acid (q.v.) that conforms to the formula (Wenninger et al., 2000):



It is also known as Salicylic Acid, Magnesium Salt; Magnesium 2-Hydroxybenzoate (Wenninger et al., 2000); 2-Hydroxybenzoic Acid Magnesium Salt (Budavari, 1989); Benzoic Acid, 2-Hydroxy-, Magnesium Salt (Wenninger et al., 2000); and Magnesium, Bis(2-Hydroxybenzoato-O^1,O^2)- (Gennaro, 1990).

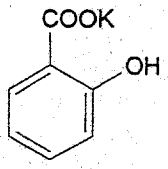
MEA-Salicylate (CAS No. 59866-70-5) is the monoethanolamine salt of Salicylic Acid (q.v.) that conforms to the formula (Wenninger et al., 2000):



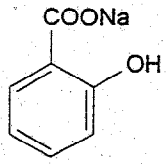
It is also known as Ethanolamine Salicylate; Salicylic Acid, Monoethanolamine Salt; Monoethanolamine 2-Hydroxybenzoate; and Benzoic Acid, 2-Hydroxy-, Monoethanolamine Salt (Wenninger et al., 2000).

Potassium Salicylate (CAS No. 578-36-9) is the potassium salt of Salicylic Acid (q.v.) that is also known as Salicylic Acid, Potassium Salt;

Potassium 2-Hydroxybenzoate; and Benzoic Acid, 2-Hydroxy-, Potassium Salt (Wenninger et al., 2000). It conforms to the formula (Wenninger et al., 2000):

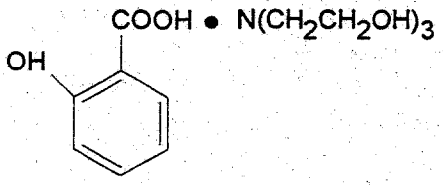


Sodium Salicylate (CAS No. 54-21-7) is the sodium salt of Salicylic Acid that conforms to the formula (Wenninger et al., 2000):



It is also known as Sodium Salicylic Acid; Salicylic Acid, Sodium Salt; Sodium o-Hydroxybenzoate; o-Hydroxybenzoic Sodium Salt (Lewis, 1993a); 2-Hydroxybenzoic Acid, Monosodium Salt (Wenninger et al., 2000; Lewis, 1993a; Budavari, 1989); and Benzoic Acid, 2-Hydroxy-, Monosodium Salt (Wenninger et al., 2000).

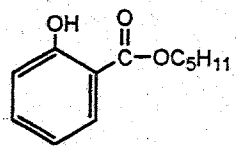
TEA-Salicylate (CAS No. 2174-16-5) is the triethanolamine salt of Salicylic Acid that conforms to the formula (Wenninger et al., 2000):



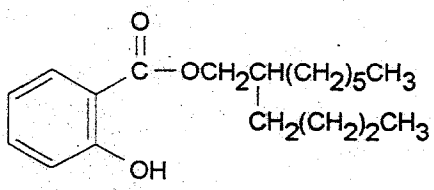
It is also known as Triethanolamine Salicylate; Trolamine Salicylate; 2-Hydroxybenzoic Acid, Compd. with 2,2',2"-Nitrilotris[Ethanol] (1:1); and Benzoic Acid, 2-Hydroxy-, Compd. with 2,2',2"-Nitrilotris[Ethanol] (1:1) (Wenninger et al., 2000).

Salicylic Acid Esters

Amyl Salicylate is not addressed in this report because its only current use is as a fragrance ingredient; it is the ester of amyl alcohol and salicylic acid that conforms to the formula (Wenninger et al., 2000):

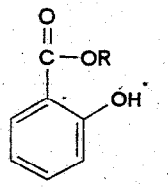


Butyloctyl Salicylate (CAS No. not available) is the compound that conforms to the formula (Wenninger et al., 2000):



It is also known as Salicylic Acid, 2-Butyloctyl Ester (Wenninger et al., 2000).

C12-15 Alkyl Salicylate (CAS No. not available) is the ester of C12-15 alcohols (q.v.) and Salicylic Acid that conforms to the formula (Wenninger et al., 2000):

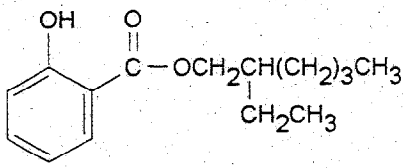


where R represents the C12-15 alkyl group

Capryloyl Salicylic Acid is the ester of Salicylic Acid (q.v.) and caprylic acid (q.v.) (Wenninger et al., 2000). (CAS No. and structure not available.)

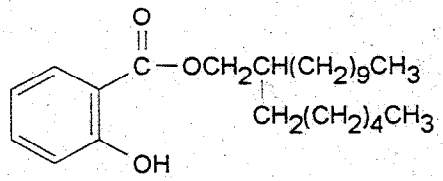
Ethylhexyl Salicylate (CAS No. 118-60-5) is the ester of 2-ethylhexyl alcohol and Salicylic Acid that is also known as Benzoic Acid, 2-Hydroxy-, 2-Ethylhexyl Ester; 2-Ethylhexyl 2-Hydroxybenzoate; Ethyl hexyl salicylate; 2-Ethylhexyl Salicylate; Octyl Salicylate; and Salicylic Acid, 2-Ethylhexyl Ester (Wenninger et

al., 2000). It conforms to the formula (Wenninger et al., 2000):



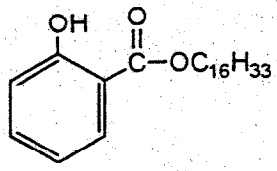
Because this cosmetic ingredient was previously known as Octyl Salicylate (Wenninger and McEwen, 1997) and many of the references refer to Octyl Salicylate, this ingredient will be identified as Ethylhexyl (Octyl) Salicylate in the text. Headings will refer to Ethylhexyl Salicylate, the current accepted cosmetic ingredient name.

Hexyldodecyl Salicylate (CAS No. not available) is the compound that conforms to the formula (Wenninger et al., 2000):



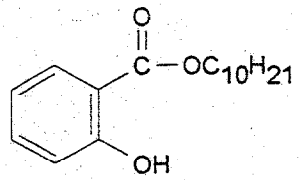
It is also known as Salicylic Acid, 2-Hexyldodecyl Ester (Wenninger et al., 2000).

Isocetyl Salicylate (CAS No. not available) is the ester of isocetyl alcohol (q.v.) and Salicylic Acid (q.v.) that conforms to the formula (Wenninger et al., 2000):

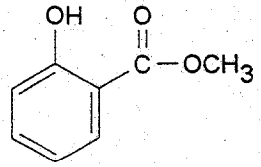


It is also known as Salicylic Acid, Isocetyl Ester (Wenninger et al., 2000).

Isodecyl Salicylate (CAS No. not available) is also known as Salicylic Acid, Isodecyl Ester (Wenninger et al., 2000). It is the ester of branched chain decyl alcohols and Salicylic Acid that conforms to the formula (Wenninger et al., 2000):



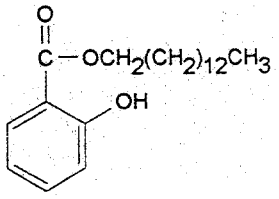
Methyl Salicylate (CAS No. 119-36-8) is the ester of methyl alcohol and Salicylic Acid that conforms to the formula (Wenninger et al., 2000):



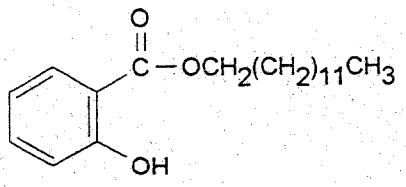
It is also known as Salicylic Acid, Methyl Ester (Lewis, 1993a); Methyl 2-Hydroxybenzoate; Benzoic Acid, 2-Hydroxy-, Methyl Ester; (Wenninger et al., 2000); 2-Hydroxybenzoic Acid, Methyl Ester (Wenninger et al., 2000; Lewis, 1993a; Budavari, 1989); o-Hydroxybenzoic Acid, Methyl Ester; 2-Methoxybenzoic Acid; o-Methoxybenzoic Acid; Methyl-o-Hydroxybenzoate; Natural Wintergreen Oil; Synthetic Wintergreen Oil (Lewis, 1993a); Oil of Wintergreen (Wenninger et al., 2000; Lewis, 1993a); Birch Oil, Sweet (Wenninger et al., 2000); Sweet Birch Oil (Wenninger et al., 2000; Lewis, 1993a; 1993b; Budavari, 1989); Wintergreen Oil; Betula Oil; Teaberry Oil (Lewis, 1993a; Budavari, 1989); Gaultheria Oil (Lewis, 1993b; Grant, 1972); Gaultheria Oil, Artificial; and o-Anisic Acid (Lewis, 1993a).

Myristyl Salicylate (CAS No. 19666-17-2) is the ester of myristyl alcohol and Salicylic Acid that is also known as Tetradecyl Salicylate; Salicylic Acid, Tetradecyl Ester; Tetradecyl 2-Hydroxybenzoate; 2-Hydroxybenzoic Acid, Tetradecyl Ester;

and Benzoic Acid, 2-Hydroxy-, Tetradecyl Ester (Wenninger et al., 2000). Myristyl Salicylate conforms to the formula (Wenninger et al., 2000):



Tridecyl Salicylate (CAS No. 19666-16-1) is the ester of tridecyl alcohol (q.v.) and Salicylic Acid (q.v.) that conforms to the formula (Wenninger et al., 2000):



It is also known 2-Hydroxybenzoic Acid, Tridecyl Ester and Benzoic Acid, 2-Hydroxy-, Tridecyl Ester (Wenninger et al., 2000).

PHYSICAL AND CHEMICAL PROPERTIES

Physical and chemical properties of Salicylic Acid and Calcium, Magnesium, Potassium, Sodium, Methyl, and Ethylhexyl (Octyl) Salicylate are described in Table 1. Salicylic Acid and its salts are powders, but its esters appear to be liquids.

MANUFACTURE AND PRODUCTION

Salicylic Acid is found in the bark of the willow tree, *Salix alba* (Lin and Nakatsui, 1998). It can be prepared using the Kolbe-Schmidt process in which carbon dioxide is reacted with sodium phenolate under pressure at approximately 130° C to form Sodium Salicylate, which is then treated with mineral acid (Gennaro, 1990).

Ethylhexyl Salicylate [Ethylhexyl (Octyl) Salicylate] is prepared from 2-ethylhexanol and Salicylic Acid by azeotropic esterification (Anonymous, 1976).

Magnesium Salicylate is prepared by reacting magnesium oxide in a hot mixture of isopropanol and water, and the hydrated salt crystallizes on cooling (Gennaro, 1990).

Methyl Salicylate is present in wintergreen leaves, *Gaultheria procumbens* L., *Ericacese*, and in the sweet birch bark, *Betula lenta* L., *Betulaceae,* (USP, 1995b). Methyl Salicylate can be produced synthetically or obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* L. or from the bark of *Betula lenta* L. (USP, 1995b). Methyl Salicylate is synthesized by esterification of Salicylic Acid with methyl alcohol (Speer, 1979).

Sodium Salicylate is mixed with sufficient distilled water to form a paste, then sufficient pure sodium carbonate is added in small portions to neutralize all but a fraction of the Salicylic Acid (Gennaro, 1990). The resulting solution is filtered, and the filtered solution is evaporated.

ANALYTICAL METHODS

A salicylate test system, a device intended to measure salicylates in humans, has been used in the diagnosis and treatment of salicylate overdose and in monitoring salicylate concentrations to ensure appropriate therapy (21 CFR 862.3830).

Salicylic Acid has been determined in human urine using colorimetry (Farid et al., 1975), in human serum using a liquid-liquid chromatographic system with a limit of detection of 1 ng (corresponding to 40 ppb Salicylic Acid in serum) (Terweij-Groen et al., 1978) and with spectrofluorometric methods (Birmingham et al., 1979), simultaneously with aspirin in plasma using gas-liquid chromatography (Walter et al., 1974), in human plasma and urine using gradient reversed-phase high-performance liquid chromatography (HPLC), with limits of detection of 0.2 and 5 µg/ml

Table 1. Physical and Chemical Properties of Salicylic Acid And Some Salicylates

Property	Description	Reference
	SALICYLIC ACID	
Physical Characteristics	Needles with water and monoclinic prisms with alcohol	Lide, 1993
	White powder with an acrid taste	Lewis, 1993b
	White, fine, needle-like crystals or a fluffy, white, crystalline powder; the synthetic form is white and odorless with a sweetish, afterward acrid, taste	Gennaro, 1990
	Acicular crystal or crystalline powder that is virtually odorless	Nikitakis and McEwen, 1990a
Molecular Formula	$C_7H_6O_3$	Gennaro, 1990; Budavari, 1989
Molecular Weight	138.12	Lide, 1993; Gennaro, 1990
Boiling Point	211°C (20 mm Hg); sublimes at 76°C	Lewis, 1993b; Budavari, 1989
Melting Point	158-161°C	USP*, 1995a; Nikitakis and McEwen, 1990a
	157-159°C	Budavari, 1989; Kabara, 1984
Solubility	Soluble in acetone, oil of turpentine, alcohol, ether, benzene; slightly soluble in water	Lewis, 1993b
	Soluble in ethanol, acetone, chloroform, ether, and boiling water; only slightly soluble in cold water	Nikitakis and McEwen, 1990a
	Solubility in water is increased by the addition of sodium phosphate, borax, alkali acetates or citrates	Kabara, 1984
Octanol/Water Partition Coefficient (log P)	1.96	Sheu et al., 1975
	2.25	Higo et al., 1995
Refractive Index	1.565	Lide, 1993
Density	1.443 (20°/4°C)	Lide, 1993; Lewis, 1993a
pH of satd aq soln	2.4	Budavari, 1989
Flash Point	315°F	Sax, 1979
Stability	Discolors in sunlight	Nikitakis and McEwen, 1990a
	Emits acrid smoke and irritating fumes when heated to decomposition	Lewis, 1993a
	Decomposes into phenol and CO_2 when rapidly heated at atmospheric pressure	Kabara, 1984
Reactivity	Incompatible with iron salts, spirit nitrous ether, lead acetate, and iodine; colored reddish by ferric salts	Budavari, 1989
Autoignition Temp	1013°F	Sax, 1979
	CALCIUM SALICYLATE	
Physical Characteristics	Colorless crystals	Grant, 1972
Molecular Formula	$Ca(OCC_6H_4OH)_2 \cdot 2H_2O$	Grant, 1972
Molecular Weight	350.20	Grant, 1972
Solubility	Soluble in carbonated water	Grant, 1972

Table 1 (con't). Physical and Chemical Properties of Salicylic Acid And Some Salicylates

Property	Description	Reference
	MAGNESIUM SALICYLATE	
Physical Characteristics	White to slightly pink, free-flowing crystalline powder with no or a faint characteristic odor	Gennaro, 1990
	Tetrahydrate, white, odorless, efflorescent, crystalline powder	Budavari, 1989
Molecular Formula	$C_{14}H_{10}MgO_6$	Budavari, 1989
Molecular Weight	298.54 (anhydrous)	USP, 1995a
	298.53 (anhydrous)	Gennaro, 1990
	POTASSIUM SALICYLATE	
Physical Characteristics	White odorless powder	Budavari, 1989
	White crystals	Grant, 1972
Molecular Formula	$C_7H_5KO_3$	Budavari, 1989
Molecular Weight	176.21	Budavari, 1989
Solubility	Very soluble in water and alcohol	Budavari, 1989
Reactivity	Becomes pink on exposure to light	Budavari, 1989
	SODIUM SALICYLATE	
Physical Characteristics	Colorless or faintly pink amorphous or microcrystalline powder or scales that has no or a faint characteristic odor and has a sweet, saline taste	Gennaro, 1990
	White odorless crystals, scales, or powder	Budavari, 1989
Molecular Formula	$C_7H_5NaO_3$	Budavari, 1989
Molecular Weight	160.11	USP, 1995a
Solubility	Soluble in water	Grant, 1972
pH of aq soln	5-6	Budavari, 1989
Reactivity	Incompatible with alkalies or iron; darkens	Gennaro, 1990
	Becomes pinkish on long exposure to light; incompatible with ferric salts, lime water, spirit nitrous ether, mineral acids, iodine, lead acetate, silver nitrate, sodium phosphate in powder	Budavari, 1989
	METHYL SALICYLATE	
Physical Characteristics	Colorless, yellowish, or reddish liquid with the odor and taste of wintergreen	National Academy of Sciences (NAS), 1996
	Volatile oil having the characteristic odor and taste of wintergreen	Nikitakis and McEwen, 1990a
	Colorless, yellowish, or reddish oily liquid with the odor and taste of gaultheria	Budavari, 1989
Molecular Formula	$C_8H_8O_3$	Budavari, 1989
Molecular Weight	152.15	USP, 1995b; Lide, 1993
	152.14	Sax, 1979
Boiling Point	223.3°C	Lide, 1993; Sax, 1979
	220-224°C	Budavari, 1989
Melting Point	-8°C	Lide, 1993
	-8.6°C	Budavari, 1989
Solubility	Soluble in alcohol and glacial acetic acid; slightly soluble in water	NAS, 1996
	Soluble in alcohol and ether	Lide, 1993

Table 1 (con't). Physical and Chemical Properties of Salicylic Acid And Some Salicylates

Property	Description	Reference
	METHYL SALICYLATE (con't)	
	Soluble in chloroform and ether; slightly soluble in water; miscible with alcohol and glacial acetic acid	Budavari, 1989
	Insoluble in water	Grant, 1972
log P	1.45	Sheu et al., 1975
	2.46	Higo et al., 1995
Index of Refraction	1.5350-1.5380 (20°C)	USP, 1995b; Nikitakis and McEwen, 1990a
Acid Value	0.5% maximum	Nikitakis and McEwen, 1990a
Specific Gravity	Synthetic: 1.180-1.185 (25°/25°C); Natural: 1.176-1.182 (25°/25°C)	USP, 1995b; Nikitakis and McEwen, 1990a
	Natural: 1.180	Budavari, 1989
Angular Rotation	Synthetic and from *Betula*: inactive; Natural: -1.5° maximum	USP, 1995b
Flash Point	210°F (closed cup)	Budavari, 1989
	214°F (closed cup)	Sax, 1979
Reactivity	Slight fire hazard when exposed to heat or flame; can react with oxidizing materials	Sax, 1979
Autoignition Temp	850°F	Sax, 1979
	ETHYLHEXYL (OCTYL) SALICYLATE	
Physical Characteristics	Clear, pale, straw-colored liquid having a faint characteristic odor	Nikitakis and McEwen, 1990b
Molecular Weight	250	Treffel and Gabard, 1996
log P	6.02	Treffel and Gabard, 1996
Solubility	Insoluble in water	Haarmann and Reimer, 1992
Saponification Value	200 minimum	Nikitakis and McEwen, 1990b
Specific Gravity	1.103-1.022 (25°/25°C)	Nikitakis and McEwen, 1990b
	BUTYLOCTYL SALICYLATE	
Boiling Point	Decomposes at 251-334°C	Huntingdon Life Sciences, 1998a
Freezing Point	< -25°C	Huntingdon Life Sciences, 1998a
Solubility	$<2.84 \times 10^{-5}$ g/l at 20°C	Huntingdon Life Sciences, 1998a
log P	>6.2 (20°C)	Huntingdon Life Sciences, 1998a
Density	0.971 (D^{20}_4)	Huntingdon Life Sciences, 1998a
Vapor Pressure	14 Pa at 25°C	Huntingdon Life Sciences, 1998a
Flash Point	166°C	Huntingdon Life Sciences, 1998a
Reactivity	Not explosive	Huntingdon Life Sciences, 1998a
Autoignition Temp	263°C	Huntingdon Life Sciences, 1998a

in plasma and urine, respectively (Vree et al., 1994a), and in human serum and urine using micellular electrokinetic chromatography, capillary zone electrophoresis, and capillary isotachophoresis (Caslavska et al., 1993). Salicylic Acid was measured in rat cerebrospinal fluid and striatal tissue using HPLC with ultraviolet (UV) absorbance and electrochemical detection (Sloot and Gramsbergen, 1995). HPLC with spectrophotometry was used to identify and quantify Salicylic Acid in biological fluids without organic extraction, with a limit of detection of 3.89 µmol/l (Coudray et al., 1996), and HPLC with UV detection of Salicylic Acid in biological fluids was also used by Krivosíková et al. (1996).

HPLC was used to determine the presence of Salicylic Acid in aspirin, with a limit of detection of 5 ng (Salako et al., 1989), and Salicylic Acid was quantified in aspirin powders and its dosage forms using reversed-phase HPLC, with Salicylic Acid quantities as low as 0.1 µg being assayed (das Gupta, 1980). Second-derivative spectroscopy and HPLC have also been used to determine Salicylic Acid in aspirin, with limits of detection of 1.27 and 1.93 µg/ml, respectively (Torrado et al., 1994), as has a spectrofluorometric method, with sensitivity of the order of 10^{-8} g (Villari et al., 1994).

Simultaneous analysis of Salicylic Acid and aspirin in aspirin products was determined using reversed-phase HPLC with UV and fluorescence detection (Kirchhoefer, 1980) and in pharmaceutical tablet preparations with two multicomponent UV-spectrophotometric methods using principal component regression and classical least square algorithm and by an assay based on second-derivative spectroscopy (Glombitza and Schmidt, 1994). Salicylates in buffer solutions have been determined using a voltametric method (Moore et al., 1995). Salicylic Acid was determined in an aerosol foot powder with gas chromatography (Palermo and Lundberg, 1979).

Methyl Salicylate has been determined using HPLC (Boehnlein et al., 1994).

TEA-Salicylate has been assayed by thin-layer chromatography and nuclear magnetic resonance (Rabinowitz and Baker, 1984).

COMPOSITION/IMPURITIES

Salicylic Acid
U.S. Pharmacopeia (USP)-grade Salicylic Acid is to contain not less than 99.5 and not more than 101.0% $C_7H_6O_3$, calculated on the dry basis (USP, 1995a).

Magnesium Salicylate
USP-grade Magnesium Salicylate is to contain not less than 98.0 and not more than 103.0% $C_{14}H_{10}MgO_6 \cdot 4H_2O$, and it should contain less than 0.004% heavy metals (USP, 1995a).

Methyl Salicylate
USP-grade Methyl Salicylate is to contain not less than 98.0 and not more than 100.5% $C_8H_8O_3$, and it should contain less than 0.004% heavy metals (USP, 1995b). Methyl Salicylate is to contain no more than 3 ppm arsenic (as As) or 10 ppm lead (as Pb) (Nikitakis and McEwen, 1990).

Sodium Salicylate
USP-grade Sodium Salicylate is to contain not less than 99.5 and not more than 100.5% $C_7H_5NaO_3$, calculated on the anhydrous basis, and it should contain less than 0.003% heavy metals (USP, 1995a).

ULTRAVIOLET ABSORBANCE

Salicylic Acid
In the UVB range, Salicylic Acid has a peak absorbance at approximately 305-310 nm (Glombitza and Schmidt, 1994; Komreich et al., 1996). Coudray et al. (1996) reported maximal absorption at 295 nm.

Ethylhexyl Salicylate
Ethylhexyl (Octyl) Salicylate has an absorption band at 280-320 nm, with moderate absorptivity (Gennaro, 1990). An aq. solution of Ethylhexyl Salicylate was illuminated with light from a solar simulator and evaluated for singlet molecular oxygen formation (Allen et al., 1996). Furfuryl alcohol, a chemical trap for singlet oxygen, was added to the solution. No loss of furfuryl alcohol was observed, indicating that no singlet oxygen was formed, and Ethylhexyl Salicylate did not produce any other toxic oxidant species capable of consuming furfuryl alcohol.

USE

COSMETIC

The ingredients reviewed in this report function in cosmetic formulations as reported in Table 2 (Wenninger et al., 2000).

Information on use of these ingredients in cosmetic formulations is available both from the Food and Drug Administration (FDA) and the Cosmetic, Toiletry, and Fragrance Association (CTFA). Information reported to FDA by manufacturers in 1998 listed the following uses: Salicylic Acid in a total of 107 cosmetic formulations, Sodium Salicylate in seven formulations, TEA-Salicylate in five formulations, Capryloyl Salicylic Acid in five formulations, Isodecyl Salicylate in three formulations, Methyl Salicylate in 25 formulations, Ethylhexyl (Octyl) Salicylate in 83 formulations, and Tridecyl Salicylate in two formulations (FDA, 1998). The product categories in which these ingredients were reportedly used are shown in Table 3. CTFA additionally reported use of Isocetyl Salicylate and Butyloctyl Salicylate (CTFA, 2000). Neither FDA nor CTFA reported uses of Butyloctyl, Calcium, C12-15 Alkyl, Hexyldodecyl, Isocetyl, Magnesium, MEA-, Myristyl, and Potassium Salicylate (FDA, 1998; CTFA, 2000).

Concentration of use data submitted by industry (CTFA, 2000) stated that Salicylic Acid was used at concentrations of ≤3%, Butyloctyl Salicylate was used at concentrations of ≤5%, Capryloyl Salicylic Acid was used at concentrations of ≤1%, Isocetyl Salicylate was used at concentrations of ≤5%, Methyl Salicylate was used at concentrations of ≤0.6%, Ethylhexyl (Octyl) Salicylate was used at concentrations of ≤8%, Sodium Salicylate was used at concentrations of ≤2%, TEA-Salicylate was used at concentrations of ≤0.75%, and Tridecyl Salicylate was used at a concentration of 0.01%. The product categories in which these ingredients reportedly were used and the concentrations of use for each are shown in Table 3.

INTERNATIONAL

Salicylic Acid and its salts appear in Annex VI, Part 1, of the Cosmetics Directive of the

Table 2. Functions in Cosmetic Formulations

Ingredient	Function
Salicylic Acid	antiacne agent
	antidandruff agent
	corn/callus/wart remover
	denaturant
	hair conditioning agent
	skin conditioning agent - miscellaneous
Butyloctyl Salicylate	hair conditioning agent
	skin conditioning agent - miscellaneous
	solvent
Calcium Salicylate	preservative
C12-15 Alkyl Salicylate	skin conditioning agent - miscellaneous
Capryloyl Salicylic Acid	skin conditioning agent - miscellaneous
Hexyldodecyl Salicylate	hair conditioning agent
	skin conditioning agent - miscellaneous
	solvent
Isocetyl Salicylate	skin conditioning agent - miscellaneous
Isodecyl Salicylate	skin conditioning agent - miscellaneous
Magnesium Salicylate	preservative
MEA-Salicylate	preservative
Methyl Salicylate	denaturant
	external analgesic
	flavoring agent
	fragrance ingredient
Myristyl Salicylate	not reported
Ethylhexyl Salicylate	fragrance ingredient
	sunscreen agent
	UV light absorber
Potassium Salicylate	cosmetic biocide
	preservative
Sodium Salicylate	denaturant
	preservative
TEA-Salicylate	sunscreen agent
	ultraviolet light absorber
Tridecyl Salicylate	skin conditioning agent - miscellaneous

Table 3. Ingredient Usage as a Function of Product Type

Ingredient	Product Type (Total number reported to FDA) (FDA, 1998)	Number of Formulations With the Ingredient (FDA, 1998)	Concentration of use (CTFA, 2000)
SALICYLIC ACID			
	Eye lotion (18)	-	2%
	Other eye makeup preparations (120)	2	0.2%
	Hair conditioners (636)	4	0.1-0.2%
	Hair straighteners (63)	-	0.002%
	Permanent Waves (192)	1	
	Shampoos (non-coloring) (860)	11	0.2%
	Tonics, dressings, and other hair grooming aids (549)	10	0.2%
	Other hair preparations (276)	2	0.2%
	Hair dyes and colors (all types requiring caution statement and patch test) (1572)	-	0.1%
	Hair tints (54)	-	0.1%
	Other hair coloring preparations (59)	2	
	Blushers (all types) (238)	1	0.5%
	Face Powders (250)	1	0.2-0.6%
	Foundations (287)	2	0.5-3.0%
	Lipstick (790)	-	1%
	Makeup bases (132)	-	0.6%
	Makeup fixatives (11)	-	1%
	Other makeup preparations (135)	2	0.6%
	Nail creams and lotions (17)	-	0.2%
	Bath soaps and detergents (385)	1	0.0008-2.0%
	Deodorants (underarm) (250)	1	
	Other personal cleanliness products (291)	1	0.1%
	Skin cleansing (653)	18	0.04-3.0%
	Depilatories (28)	1	
	Face and neck preparations (excluding shaving) (263)	1	0.1-3.0%
	Body and hand preparations (excluding shaving) (796)	9	0.02-2.0%
	Foot powders and sprays (38)	3	
	Moisturizing creams, lotions, powders and sprays (769)	10	0.2-0.5%
	Night preparations (188)	1	
	Paste masks (mud packs) (255)	6	0.2%
	Skin fresheners (184)	7	0.5-3.0%
	Other skin care preparations (692)	8	0.1-3.0%
	Indoor tanning preparations (62)	-	0.1%
	Other suntanning preparations (38)	2	
	Total Salicylic Acid uses reported to FDA	**107**	

Table 3 (con't). Ingredient Usage as a Function of Product Type.

Ingredient	Product Type (Total number reported to FDA) (FDA, 1998)	Number of Formulations With the Ingredient (FDA, 1998)	Concentration of use (CTFA, 2000)
Capryloyl Salicylic Acid			
	Skin cleansing (653)	-	0.1%
	Face and neck preparations (excluding shaving) (263)	1	1.0%
	Body and hand preparations (excluding shaving) (796)	-	0.5%
	Moisturinzing creams, lotions, powders and sprays (789)	2	
	Indoor tanning preparations (62)	2	0.1%
	Total Capryloyl Salicylic Acid uses reported to FDA	**5**	
Butyloctyl Salicylate			
	Face powders (250)	-	0.5%
	Foundations (287)	-	4.0%
	Moisturinzing creams, lotions, powders and sprays (769)	-	4.0%
	Suntan gels, creams and liquids (136)	-	5.0%
	Total Butyloctyl Salicylate uses reported to FDA	**0**	
Isocetyl Salicylate			
	Face and neck preparations (excluding shaving) (263)	-	3.0%
	Suntan gels, creams and liquids (136)	-	5.0%
	Total Isocetyl Salicylate uses reported to FDA	**0**	
Isodecyl Salicylate			
	Moisturinzing creams, lotions, powders and sprays (769)	2	
	Paste masks (mud packs) (255)	1	
	Total Isodecyl Salicylate uses reported to FDA	**3**	
Methyl Salicylate			
	Dentifrices (38)	4	0.03%
	Mouthwashes and breath fresheners (49)	10	0.08-0.2%
	Other oral hygiene products (6)	-	0.2%
	Bath soaps and detergents (385)	-	0.0001%
	Bath oils, tablets and salts (124)	1	
	Body and hand preparations (excluding shaving) (796)	1	0.05%
	Skin cleansing (653)	1	
	Douches (5)	2	
	Foot powders and sprays (35)	-	0.02%
	Hair conditioners (636)	1	
	Shampoos (non-coloring) (860)	1	
	Tonics, dressings and other hair grooming aids (549)	1	
	Paste masks (mud packs) (255)	1	0.6%
	Skin fresheners (184)	1	0.1%
	Other skin care preparations (692)	1	0.02%
	Suntan gels, creams and lotions (136)	-	0.2%
	Total Methyl Salicylate uses reported to FDA	25	

Table 3 (con't). Ingredient Usage as a Function of Product Type.

Ingredient	Product Type (Total number reported to FDA) (FDA, 1998)	Number of Formulations With the Ingredient (FDA, 1998)	Concentration of use (CTFA, 2000)
Ethylhexyl Salicylate			
	Hair conditioners (636)	2	0.001-0.005%
	Hair sprays (aerosol fixatives) (261)	16	0.001-0.01%
	Other fragrance preparations (148)	2	
	Shampoos (non-coloring) (860)	1	0.001%
	Tonics, dressings and other hair grooming aids (549)	12	0.001-0.01%
	Other hair preparations (276)	4	
	Foundations (287)	1	5.0%
	Lipstick (790)	2	8.0%
	Makeup bases (132)	2	
	Other makeup preparations (135)	1	5.0%
	Basecoats and undercoats (manicuring preparations) (48)	1	0.1%
	Men's talcum (8)	-	5.0%
	Face and neck preparations (excluding shaving) (263)	-	5.0%
	Body and hand preparations (excluding shaving) (796)	2	0.5-5.0%
	Moisturizing creams, lotions, powders and sprays (769)	10	2.0-5.0%
	Other skin preparations (692)	1	
	Suntan gels, creams and lotions (136)	21	4.0-5.0%
	Indoor tanning preparations (62)	5	4.0-5.0%
	Total Ethylhexyl Salicylate uses reported to FDA	**83**	
Sodium Salicylate			
	Tonics, dressings and other hair grooming aids (549)	1	0.2%
	Other hair preparations (276)	1	
	Dentifrices (38)	2	
	Mouthwashes and breath fresheners (liquids and sprays) (49)	-	0.09-0.2%
	Other oral hygiene products (6)	-	0.2%
	Skin cleansing (653)	-	0.3%
	Face and neck preparations (excluding shaving) (263)	-	2.0%
	Body and hand preparations (excluding shaving) (796)	1	
	Moisturizing creams, lotions, powders and sprays (769)	2	
	Other skin care preparations (692)	-	2.0%
	Total Sodium Salicylate uses reported to FDA	**7**	
TEA-Salicylate			
	Foundations (287)	3	0.0001%
	Makeup bases (132)	-	0.75%
	Other personal cleanliness products (291)	-	0.0002%
	Skin cleansing (653)	-	0.0001%
	Other skin care preparations (692)	1	
	Face and neck preparations (excluding shaving) (263)	-	0.0002%
	Body and hand preparations (excluding shaving) (796)	-	0.001%
	Suntan gels, creams and liquids (136)	1	
	Total TEA-Salicylate uses reported to FDA	**5**	

Ingredient	Product Type (Total number reported to FDA) (FDA, 1998)	Number of Formulations With the Ingredient (FDA, 1998)	Concentration of use (CTFA, 2000)
Tridecyl Salicylate			
	Face and neck preparations (excluding shaving) (263)	1	
	Body and hand preparations (excluding shaving) (796)	1	0.01%
	Total Tridecyl Salicylate uses reported to FDA	**2**	

European Union, which names the preservatives which cosmetic products may contain (European Economic Community, 1998). Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate are allowed for use in cosmetics as preservatives at a maximum concentration of 5% (acid). These ingredients are not to be used in preparations for children under 3 yrs of age, except for shampoo formulations, and this warning must be printed on the label.

Salicylic Acid, Sodium Salicylate, Methyl Salicylate, and Ethylhexyl (Octyl) Salicylate are listed in the Japanese *Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci, 1997). Salicylic Acid which conforms to the standards of the *Japanese Standards of Cosmetic Ingredients (JSCI)* has precedent for use at a maximum concentration of 0.2% in all CLS categories except eyeliner preparations, in which it is not used.

Sodium Salicylate which conforms to the specifications of the *JSCI* has precedent for use at a maximum concentration (calculated as total Salicylic Acid) of 1% in cleansing preparations and of 0.2% in hair care, treatment, makeup, fragrance, suntan and sunscreen, and nail makeup preparations; it is not used in eyeliner, lip, oral, or bath preparations. Sodium Salicylate is restricted as to the per cent as total Salicylic Acid salts allowed in a formulation.

Methyl Salicylate which conforms to the specifications of the *JSCI* has precedent for use at a maximum concentration of 0.1% in all CLS categories except eyeliner preparations, in which it is not used.

Ethylhexyl (Octyl) Salicylate which conforms to the specifications of the *Japanese Cosmetic Ingredient Codex* has precedent at a maximum concentration of 10% in suntan/sunscreen preparations and of 1% in all other CLS preparations except eyeliner and bath preparations, in which it is not used. Methyl and Ethylhexyl (Octyl) Salicylate are restricted in that the total percentage of UV absorbers in a formulation shall not exceed 10%.

NON-COSMETIC

Salicylic Acid, Magnesium Salicylate, Sodium Salicylate, and Methyl Salicylate have use as indirect food additives (21 Code of Federal Regulations [CFR] 175.105; 177.1010; 178.2010). Salicylic Acid has been used in the treatment of ichthyosiform dermatoses (Van Scott and Yu, 1974). Salicylic Acid is an approved active ingredient for use in topical over-the-counter (OTC) acne drug products at concentrations of 0.5-2% (21 CFR 333.310), in OTC wart remover drug products at concentrations of 12-40% in a plaster vehicle, 5-17% in a collodion-like vehicle, and 15% in a karaya gum, glycol plaster vehicle (21 CFR 358.110), in corn and callus remover OTC drug products at concentrations of 12-40% in a plaster vehicle and 12-17.6% in a collodion-like vehicle (21 CFR 358.510), and in OTC drugs for the control of dandruff, seborrheic dermatitis, and psoriasis at a concentration of 1.8-3% (21 CFR 358.710). Labeling requirements, including directions and warnings, for wart remover drug products are found in 21 CFR 358.150 and for corn and callus remover drug products in 21 CFR 358.550.

Salicylic Acid has been present in OTC topical acne preparations (at concentrations of 2-5%), external analgesics and skin protectants used for poison ivy, oak, and sumac, and topical antifungal drug products; Calcium Salicylate has been present in OTC internal analgesic drug products; So-

dium Salicylate has been present in OTC dandruff/seborrheic dermatitis/psoriasis and digestive aid drug products; TEA-Salicylate has been present in OTC external analgesic - fever blister and cold sore, - insect bite and sting, and - poison ivy, oak, and sumac drug products (21 CFR 310.545); Methyl Salicylate has been present in OTC smoking deterrent drugs (21 CFR 310.544), boil treatment (21 CFR 310.531) dandruff/seborrheic dermatitis/psoriasis, fever blister and cold sore treatment, oral health care, and skin protectant - astringent drug products (21 CFR 545); however, currently "there is a lack of adequate data to establish general recognition of the safety and effectiveness" of these ingredients for the specified OTC uses. Any drug product intended to be taken orally that contains any salicylate ingredient, except effervescent preparations, must bear a statement warning to keep the product out of the reach of children (21 CFR 201.314).

Because of the toxicity of Methyl Salicylate, the Department of Health and Human Services regards any drug containing >5% Methyl Salicylate as misbranded under the Federal Food, Drug, and Cosmetic Act if that product does not have labeling that warns that misdirected use may be dangerous and that the product should be kept out of the reach of children (21 CFR 201.314). A traditional use of Methyl Salicylate is as a counterirritant (Green and Flammer, 1989).

Salicylic Acid is allowed for use in the removal of scar tissue from the teat canal of milk-producing cows (21 CFR 529.2090); however, a residue tolerance of 0 has been established for milk from dairy animals (21 CFR 556.590).

Salicylic Acid is used in the manufacture of aspirin (Lewis, 1993b). The amount of free Salicylic Acid allowed in aspirin is 0.1%, in uncoated aspirin tablets is 0.3%, in aspirin capsules is 0.75%, in aspirin delayed-release tablets is 2.0%, in coated aspirin tablets, buffered aspirin tablets, aspirin extended-release tablets, aspirin delayed-release capsules, and aspirin suppositories is 3.0%, and in aspirin effervescent tablets for oral solution is 8.0% (USP, 1995a).

Salicylic Acid is also used in the manufacture of salicylates and resins and as a dyestuff intermediate, prevulcanization inhibitor, analytical reagent, and fungicide (Lewis, 1993b). Sodium Salicylate is used as a preservative for paste, mucilage, glues, and hides, and Methyl Salicylate is used in perfumery (Budavari, 1989).

TEA- and Ethylhexyl (Octyl) Salicylate, while not potent sunscreens, are effective sunscreens and have extraordinary stability (Markland, 1976). TEA-Salicylate is allowed for use as an active ingredient in sunscreens at concentrations of <12%, while Ethylhexyl (Octyl) Salicylate is allowed at concentrations of <5% (FDA, 1999).

GENERAL BIOLOGY

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Absorption of salicylates from the stomach is normally quite rapid (Andrews, 1973). Salicylate is metabolized by the hepatic microsomal enzyme system, which conjugates Salicylic Acid to glycine, forming salicyluric acid (SU), and to glucuronic acid, forming salicylic acid phenolic glucuronide (SAPG) and/or salicylic acid acyl glucuronide (SAAG) (Goldsmith, 1979). Vree et al., (1994b) describe the conjugation reaction to salicylic acid acyl glucuronide as reversable if the urine is alkaline. Salicylic Acid may also be oxidized to gentisic acid (GA) which may, in turn, be conjugated with glucuronic acid to form gentisic acid phenolic glucuronide (GAPG) and/or gentisic acid acyl glucuronide (GAAG).

Figure 1 depicts these possible metabolites of Salicylic Acid, along with the several double conjugates that are possible (Vree et al., 1994b). Goldsmith (1979) states that urinary metabolites of salicylic acid obtained after percutaneous absorption of salicylate differ from those obtained after oral administration in that there is reported - more salicylate glucuronides and less salicyluric acid (SUA) and Salicylic Acid.

To assist the reader with the large amount of information available on absorption, distribution, metabolism, and excretion, a series of table have been constructed and will appear at the end of this section. Table 8a presents the information for the dermal route of administration, 8b for the oral route, 8c for administration via the oral mucosa, and 8d for parenteral administration.

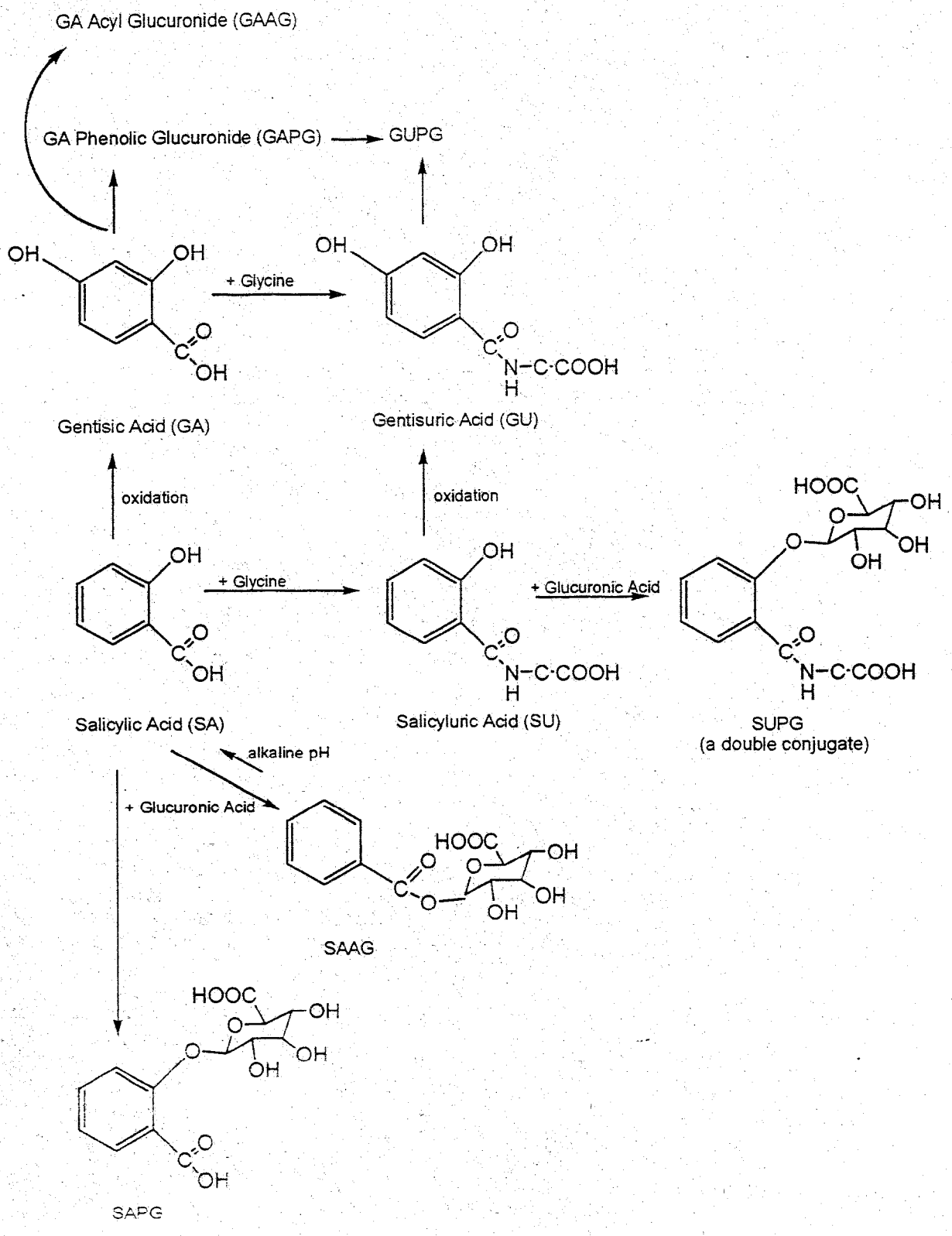


Figure Metabolites of Salicylic Acid: SAPG - Salicylic Acid Phenolic Glucuronide: SAAG - Salicylic Acid Acyl Glucuronide: SUPG - Salicyluric Acid Phenolic Glucuronide (Vree et al. 1994b).

DERMAL ROUTE OF ADMINISTRATION

Salicylic Acid

There are *in vitro* and *in vivo* animal and human data on the dermal absorption, distribution, metabolism, and excretion of Salicylic Acid.

In Vitro Animal Data

Loveday (1961) examined the *in vitro* percutaneous absorption of Salicylic Acid using whole skin from the external ears of Landrace pigs. At pH 2.2, the rate of penetration was proportional to the concentration of Salicylic Acid; the rate ranged from approximately 0.1-1.4 mg/cm^2/24 h with concentrations of 0.25-2.0 mg/ml. With a 1 mg/ml solution of Salicylic Acid, variation of the pH of the buffer solution did not affect penetration at a pH >4.4; however, at pH <4.4, a "rapid rise in rate occurred." The approximate penetration rates were 1.5, 0.75, 0.5, and 0.4 mg/cm^2/24 h at pH 2.6, 3.5, 4.2, and 4.4, respectively, and 0.375 mg/cm^2/24 h at pH 5.5 and 7.75. Addition of surfactant to the solution decreased the rate of penetration of Salicylic Acid. Treatment of excised skin with chloroform or petroleum ether for 30 min increased the rate of penetration from 0.67 mg/cm^2/24 h to 0.91 and 0.79 mg/cm^2/24 h, respectively.

The permeability coefficients for the steady-state diffusion of Salicylic Acid through hairless mouse skin was determined using six different vehicles (Sloan et al., 1983). The permeability coefficients (cm/h) (and flux [mg/cm^2/h]) for Salicylic Acid with the various vehicles were 21.2 (0.64) with oleic acid, 21.0 (0.87) with isopropyl myristate, 11.2 (1.6) with 1-octanol, 4.8 (1.09) with 1-propanol, 2.1 (0.43) with propylene glycol, and 7.9 (1.15) with formamide.

The *in vitro* percutaneous absorption and metabolism of Salicylic Acid was determined using back skin from female fuzzy rats (Bronaugh et al., 1989; 1989-1990). Approximately 5 µg/cm^2 skin of ^{14}C-Salicylic Acid, 53.8 mCi/mmol, was applied to a 0.64 cm^2 area of dermatomed skin (200 µm) in an acetone vehicle. Receptor fluid was collected at 6 h intervals for 24 h at a flow rate of 1.5 ml/h. The skin surface was then washed to remove unabsorbed test material. The metabolism of Salicylic Acid was also determined. Controls were included. To examine microsomal transformation, 100 µM Salicylic Acid, 16.6 µCi/µmol, was added to an incubation medium containing microsomal protein for 60 min.

Most of the absorbed radioactivity was found in the receptor fluid; 12.2 and 7.7% of the penetrating dose was found in the fluid and the skin, respectively. None of the absorbed Salicylic Acid was metabolized in the diffusion cell studies. It was also not metabolized when incubated with hepatic and skin microsomal preparations.

Singh and Roberts (1993) determined the penetration of Salicylic Acid through the dermis of Wistar rat skin *in vitro*. Salicylic Acid in isotonic saline buffer, pH 7.4, was applied using diffusion cells mounted on the skin. Using three samples, the permeability coefficient was 0.013 cm/h.

The percutaneous absorption of Salicylic Acid through intact hairless mouse skin was determined *in vitro* using a glass flow-through diffusion cell system (Higo et al., 1995). A 0.95 cm^2 area of skin was exposed to 1% w/v Salicylic Acid, pH 4.0. A zero-order penetration pattern was observed. Approximately 14 µmol Salicylic Acid penetrated after 10 h.

In Vivo Animal Data

The percutaneous absorption of Salicylic Acid from four different vehicles was determined using groups of 10 New Zealand white rabbits (Stolar et al., 1960). Salicylic Acid, 6%, was added to the oleaginous base petrolatum USP XV, the hydrophilic base petrolatum USP XV with water, the oil-in-water base (o/w) hydrophilic ointment USP XV, and the water-soluble base PEG ointment USP XV. The hair on the back of each animal was shaved, and 7.5 g of each ointment was applied to a 6.35 x 12.7 cm area under an occlusive patch for 9 h. Blood samples were taken hourly.

The greatest absorption was observed from the hydrophilic ointment; peak absorption was approximately 11.0 mg% at 5 h. The peak absorption concentrations with hydrophilic petrolatum with water and petrolatum were approximately 8.8 and 6.8 mg% at 6 and 4 h, respectively. Negligible absorption occurred with the PEG ointment.

Stelzer et al. (1968) used New Zealand white

rabbits to determine the absorption of Salicylic Acid from four vehicles, with and without dimethyl sulfoxide (DMSO). Fifteen percent DMSO was added to hydrophilic ointment USP XVII, hydrophilic petrolatum USP XVII, PEG ointment USP XVII, and a steareth-20 gel system, each of which contained 10% (w/w) Salicylic Acid. The ointments, with and without DMSO, were applied for 8 h under an occlusive patch to the shaved dorsal skin of four animals. Salicylate concentration was determined in blood samples that were drawn prior to dosing and at intervals for 8 h after application.

Blood salicylate concentrations peaked at 5 h (5.81 mg%) without DMSO and at 2 h (10.44 mg%) with DMSO and hydrophilic ointment, at 8 h (3.82 mg%) without DMSO and at 3 h (9.68 mg%) with DMSO and hydrophilic petrolatum, at 8 h (0.94 mg%) without DMSO and at 6 h (1.14 mg%) with DMSO and PEG ointment, and at 3 h (2.50 mg%) without DMSO and at 4 h (2.66 mg%) with DMSO and steareth-20 gel.

The absorption of reagent-grade Salicylic Acid through abdominal guinea pig skin was examined by Arita et al. (1970). The abdominal area was shaved and a recirculation apparatus was applied to determine the rate of absorption. Salicylic Acid, pH 3.0, had a constant rate of absorption (approximately 4%) at concentrations of 250, 400, and 1000 µg/ml. Salicylic Acid at a concentration of 500 µg/ml was used to examine the absorption as a function of pH. The percent absorbed from 1-6 h was 6.1, 3.3, 0.6, and 0 at pH 2, 3, 4, and 5, respectively and 0, 1.8, 8.0, and 15.5 at pH 7, 8, 9, and 10 respectively.

Marcus et al. (1970) determined the effect of pH and DMSO on the percutaneous absorption of Salicylic Acid from hydrophilic ointment USP XVII using groups of four male New Zealand white rabbits. Salicylic Acid, 10% w/w, was added to ointments that had a pH of 2.97, 4.48, 6.80, 9.23, or 10.78; a set of Salicylic Acid-containing ointments containing 15% DMSO was prepared also at each pH. Application of the non-DMSO- and DMSO-containing ointments, which was made to a 6.35 x 12.70 cm area, was varied so that two animals per pH group received the DMSO-containing and two received the non-DMSO ointment. Occlusive patches were applied to the shaved dorsal area of each animal for 7.5 h. Blood samples were taken prior to dosing and at 1.5 h intervals; the last sample was taken at 7.5 h.

Without DMSO, the blood concentrations of Salicylic Acid increased at each time interval in the pH 2.97, 4.48, and 6.80 groups; the 1.5 and 7.5 h values for these groups were 5.75 and 14.07 mg%, 2.47 and 9.98 mg%, and 2.58 and 9.34 mg%, respectively. In the pH 9.23 group, the concentration peaked at 6.0 h, and the 1.5 and 6.0 h values were 5.49 and 11.96 mg%, respectively. In the pH 10.78 group, the blood salicylate concentration peaked at 4.5 h; the 1.5 and 4.5 values were 7.03 and 16.00 mg%, respectively. The blood salicylate concentrations were greater for all animals when DMSO was added to the ointment. With DMSO, the concentration peaked at 6.0 h in the pH 2.97 and 4.48 groups; the 1.5 and 6.0 h values for these groups were 13.68 and 21.12 mg% and 8.31 and 12.73 mg%, respectively. The blood salicylate concentrations peaked at 4.5 h in the pH 6.80 and 9.23 groups; the 1.5 and 4.5 h values for these groups were 10.39 and 15.24 mg% and 8.67 and 16.70 mg%, respectively. In the pH 10.78 group, the salicylate concentration peaked at 3.0 h, and the 1.5 and 3.0 h values were 11.32 and 17.96 mg%, respectively.

Male Sprague-Dawley rats were used to determine the effect of pH on dermal absorption (Siddiqi and Ritschel, 1972). The tails of the animals were immersed in a Salicylic Acid solution containing 5% ethanol that had a pH of 2, 3, 6, or 8. At pH 2, the total amount absorbed was 0.64 µg/mm^2/h and the k_a was 2.7725/h; the degree of ionization (α) was 9.678%. At pH 3, the total amount absorbed was 0.33 µg/mm^2/h and the k_a was 2.6157/h; the α was 51.726%. At pH 6 and 8, no Salicylic Acid was absorbed; the α's were 99.906 and 99.999%, respectively.

The absorption of 3% Salicylic Acid in water, 50% ethanol, and 75% ethanol was determined using guinea pigs (number per group not specified) (Yankell, 1972). Fifty µl of ^{14}C-Salicylic Acid (0.025 µCi/ml) in each vehicle was applied to a 1.5 x 1.5 cm area of clipped skin on the back of each animal for 1 h. The animals were killed, and the skin was removed and tape-stripped 30 times. Absorption was greatest from the 75% ethanol vehicle, followed by 50% ethanol and then water; a total of 106.1, 80.0, and 56.9% of the applied dose, respectively, was recovered. Most of the

radioactivity was found in tape strips 1-5; 89.3, 76.3, and 44.9% of the applied dose in 75% ethanol, 50% ethanol, and water, respectively, were recovered in these strippings.

Yankell (1972) then determined the distribution of Salicylic Acid in 75% ethanol. Three guinea pigs were each dosed with 0.2 ml 3% ^{14}C-Salicylic Acid (8.8 µCi) in 75% ethanol on a 3 x 2 cm site on the lower back. After 24 h, the animals were killed. Most of the radioactivity was recovered in the feces (401.3-808.5% applied dose/g x 10^3) followed by the treated back muscle (161.1-686.3 % applied dose/g x 10^3). The amount recovered in the kidneys and the liver was 20.5-36.5 and 18.1-30.3 % applied dose/g x 10^3, respectively.

The percutaneous absorption of Salicylic Acid through damaged guinea pig skin was studied using a recirculation apparatus (Washitake et al., 1973). After the abdominal skin of male guinea pigs was clipped and the stratum corneum removed, a glass vessel was attached and used for continuous recirculation and the amount of Salicylic Acid, 500 µg/ml and pH 3.0, absorbed was calculated from the concentration remaining in the solution. Also, concentrations of 250, 500 and 1000 µg/ml Salicylic Acid at pH 3.0 and 500 µg/ml at a pH of 2, 3, 4, 5, or 6 were used to determine the effect of concentration and pH, respectively, on absorption.

The absorption rate of 500 µg/ml Salicylic Acid from the recirculating solution was 79.4% for damaged skin; the disappearance of Salicylic Acid from the solution was linear from the start of exposure. (This was 10 times the rate through intact skin; disappearance from intact skin was linear 1 h after the start of exposure.) The rate of absorption from the recirculating solution was independent of concentration, but it did increase with an increasing fraction of un-ionized form.

The amount of drug retained in damaged guinea pig skin after various exposure times was then determined. The animals were exposed to 500 µg/ml Salicylic Acid, pH 3.0, for 0.5, 1.0, 3.0, 4.5, or 6.0 h, and then killed. The test area was wiped and the skin isolated to the corium. A peak in the amount of Salicylic Acid reserved in the skin was observed after 0.5-1 h. The researchers attributed these results to an increase in percutaneous absorption and rapid decrease in concentration in the test solution due to removal of the stratum corneum and a rapid decrease in skin concentrations because of the decrease of Salicylic Acid in the solution. Varying the concentration of Salicylic Acid from 250-1000 µg/ml resulted in similar patterns of retention. Varying the pH from 3-6, the peak of the amount reserved became "lower and broader" with a decreasing fraction of unionized Salicylic Acid, and the time required to reach a peak had "a later trend".

The time-course of the disappearance of Salicylic Acid from damaged guinea pig skin was also investigated. Animals were killed 0.5, 1, 2, 4, and 24 h after 1 h of recirculation of 500 µg/ml Salicylic Acid, pH 3.0. Again, the test area was washed and the skin isolated to the corium. The amount of Salicylic Acid reserved in damaged skin rapidly decreased in time; after 4 h, only trace amounts were found (Washitake et al., 1973.)

Groups of eight rabbits were used to determine the dermal absorption of Salicylic Acid (Panse et al., 1974). Patches containing 5 g of a Salicylic Acid salve (36.2 mmol/100 g) were applied for 6 h; urinary excretion of Salicylic Acid was measured. Approximately 5.50 and 11.08% of the dose was excreted in the urine after 24 and 48 h, respectively.

Washitake et al. (1975) examined the percutaneous absorption of Salicylic Acid from four vehicles using a recirculation apparatus attached to the shaved abdomen of guinea pigs. Doses of 500 µg/ml Salicylic Acid in hexadecyl alcohol, oleic acid, or isopropyl myristate and of 75, 150, and 300 µg/ml in liquid paraffin were used, as was intact skin and skin damaged by tape stripping. The animals were killed at various intervals up to 6 h after recirculation, and the abdominal skin was removed and analyzed.

Using intact skin, 14.6, 1.7, 1.6, and 1.5% of the Salicylic Acid was absorbed from liquid paraffin, isopropyl myristate, hexadecyl alcohol, and oleic acid, respectively, during 1-6 h. With damaged skin, the k_a during 1-6 h was approximately 10 times greater. The amount of Salicylic Acid retained in damaged skin was less than that retained in intact skin; however, with damaged skin, the amount of Salicylic Acid in the recirculating solution decreased with time (to 60% at 6 h) and this could be the reason for the decrease in retention. No saturation phenomenon

Table 4. Peak Blood Salicylate Values in Rabbits Treated Topically with Salicylic Acid in Various Formulations (Shen et al., 1976)

Test Article	Peak Value (mg %)	Time of Peak Value (h)
Salicylic Acid (SA)	3	7
SA + DMSO	5.5	2
SA + DMSO + Poloxamer 182	11.5	2
SA + DMSO + Poloxamer 184	7	3
SA + DMSO + Poloxamer 231	11.5	2
SA + DMSO + Oleth -2	12.5	2
SA + DMSO + Oleth-20	7.5	1
SA + DMSO + Laureth-4	12	3
SA + DMSO + Sorbitan Laurate	12.5	3
SA + DMSO + Sorbitan Palmitate	12	2
SA + DMSO + Sorbitan Trioleate	12.5	2
SA + DMSO + Polysorbate 20	6.5	2
SA + DMSO + Polysorbate 40	7	1
SA + DMSO + Polysorbate 60	7.5	1
SA + DMSO + PEG-8 Stearate	5.5	3

was observed with absorption from liquid paraffin, suggesting that absorption was via simple passive transport. With all vehicles, the Salicylic Acid concentration of the recirculating solutions decreased, following first-order kinetics.

Washitake et al. (1975) also determined *in vitro* the adsorption of Salicylic Acid in each vehicle using excised guinea pig abdominal skin. The amount adsorbed from liquid paraffin, isopropyl myristate, hexadecyl alcohol, and oleic acid was 3.56, 2.26, 1.57, and 0.73 mg, respectively.

New Zealand white rabbits were also used to determine the percutaneous absorption of Salicylic Acid with and without DMSO and with and without nonionic surfactants (Shen et al., 1976). Five g of white petrolatum ointments consisting of 10% (w/w) Salicylic Acid, 10% Salicylic Acid and 10% (w/w) DMSO, or 10% Salicylic Acid, 10% DMSO, and 10% (w/w) of the surfactants were each applied to the shaved dorsal skin of two rabbits under an occlusive patch for 8 h. Blood samples, which were taken prior to and 30 min and hourly for 8 h after application, were analyzed for salicylate content. The approximate peak blood salicylate values and times are summarized in Table 4 above.

The effect of daily and weekly dermal applications, as well as the effect of concentration, on the absorption of Salicylic Acid was determined using female Wistar rats (Roberts and Horlock, 1978). Salicylic Acid, 1, 5, or 10%, in hydrophilic ointment was applied for 7.5 h to a 3 cm^2 shaved area of the flank under an occlusive patch. Application was as a single dose, repeated daily for 5 days, or repeated weekly for 4 wks. At least three animals were used per group. At the end of dosing, treated skin was excised, the appropriate ointment was applied to the epidermis, and it was placed in a diffusion cell. The penetration flux of Salicylic Acid through excised skin was compared to that of Salicylic Acid through dimethicone (an inert membrane).

With a single application, 1, 5, and 10% Salicylic Acid had a mean penetration flux of 0.014, 0.061, and 0.078 mg/cm^2/h, respectively. The ratio of the penetration fluxes of Salicylic Acid through skin vs. through dimethicone decreased with increasing concentrations of Salicylic Acid. With weekly dosing, the penetration flux of 1% Salicylic Acid remained constant during wks 1-4, but it

decreased with 5 and 10% Salicylic Acid. Also with weekly dosing, a significant difference was observed in penetration fluxes with 5 and 10% Salicylic Acid. Repeated daily doses of 1, 5, or 10% Salicylic Acid resulted in signficant differences in penetration flux between all concentrations. With 5 and 10% Salicylic Acid, an increase in the penetration flux was observed after 2 days; the flux decreased after day 3. With 1%, the flux increased slightly until day 4, and then decreased.

Single and multiple dose studies were performed using four female Rhesus monkeys to determine the percutaneous absorption of Salicylic Acid (Bucks et al., 1990). In the single dose study, 4 mg/cm^2 ^{14}C-Salicylic Acid (27 mCi/mM) was applied to the clipped abdomen of each animal. The test site was washed 24 h after application. Urine was collected for 7 days following dosing. In the multiple dose study, 4 µg/cm^2 Salicylic Acid was applied to the same site daily for 14 days; radioactive Salicylic Acid was applied only on days 1 and 8. The test sites were not washed. The animals were restrained in metabolic chairs. The cumulative percentage of ^{14}C-Salicylic Acid absorbed was 59% following the single dose and 67 and 78% following the first and eighth doses, respectively, of the multiple dose study. A significant difference in cumulative absorption was not observed with single versus multiple applications.

The effect of iontophoresis on absorption of Salicylic Acid was determined using male Wistar rats (Singh and Roberts, 1993). Glass diffusion cells were attached to an area of depilated dorsal skin to apply 1 mM Salicylic Acid with 12 µCi ^{14}C-Salicylic Acid in 20 mM *N*-2-hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid (HEPES) buffer, pH 7.4. Absorption was measured with and without iontophoresis. Also, the epidermis was removed and Salicylic Acid was applied to the dermis using diffusion cells. The absorption rate constant, clearance, and percent of dose applied was 0.0028/min, 0.50 ml/h, and 22.7%, respectively, with epidermal iontophoresis and 0.0032/min, 0.58 ml/h, and 34.3% with passive dermal absorption. The concentration of Salicylic Acid was greater in the skin, dermis, and subcutaneous (s.c.) tissue below the treated site than in the plasma. The researchers concluded that direct penetration of Salicylic Acid occured only to a depth of 3-4 mm.

In a study to determine whether Salicylic Acid can bypass dermal microcirculation to reach underlying tissues, anesthetized and dead male Wistar rats were used (Singh and Roberts, 1994). On all rats, a 4 cm^2 area of the dorsum was clipped free of hair, and 80 µm of the epidermis was removed. Salicylic Acid was applied using a glass cell that was adhered to the exposed epidermis. The anesthetized animals were then killed, and the tissues below the treated site and similar tissues from the contralateral side were removed; these tissues were also removed from the dead animals.

The dermal clearances for anesthetized and dead animals were 0.58 and 0.10 ml/h, respectively. The concentration of Salicylic Acid was greater in the underlying dermis and subcutaneous tissue compared with the concentration in the plasma and similar tissues on the contralateral side. The concentration in underlying fascia were comparable to that in the plasma. At greater tissue depths, the concentration in the underlying tissues were always less than that in the plasma but comparable to that in similar tissues from the contralateral side.

In Vitro Human Data

The absorption of 5% Salicylic Acid from five different vehicles was determined *in vitro* using seven samples of human leg and/or breast skin (Flesch et al., 1955). Positive spot tests in the corium were observed after 2-4 h. Penetration was greatest with lanolin, Plastibase®, or Hydrophilic Plastibase® (Squibb) vehicle, was moderate from a carbowax vehicle, and was very slight from a petrolatum base.

In a study to evaluate percutaneous transport as a function of stratum corneum structure and lipid composition, Elias et al. (1981) measured the penetration of 5% ^{14}C-Salicylic Acid (0.4 µCi/mg) through abdominal (postmortem) and leg skin (amputation) obtained from human males. Tissue sheets were prepared and then frozen at -70°C. Samples were thawed and mounted in a diffusion cell. Radioactively labeled Salicylic Acid and unlabeled Salicylic Acid were combined to a final concentration of 5% in propylene glycol.

For both abdominal and leg skin samples, the dermal penetration of Salicylic Acid steadily increased between 10 and 24 h, after an initial

lag. Using eight samples, the mean penetration of Salicylic Acid through abdominal stratum corneum was 3.6 µmoles/cm^2/24 h (range of 0.7-9.7 µmoles/cm^2/24 h); these stratum corneum samples had an average thickness of 21.8 micron, an average of 20.6 cell layers, and a lipid content of 6.8%. Using six samples, the mean penetration of Salicylic Acid through leg stratum corneum was 5.7 µmoles/cm^2/24 h (range of 1.9-8.7 µmoles/cm^2/24 h); these stratum corneum samples had a mean thickness of 26.8 micron, an average of 22.4 cell layers, and a lipid content of only 3.0%. The difference in penetration across the two sites was not significant, although suggestive of a higher penetration in the leg sample with its lower lipid content.

The horny layer of excised human skin and a three-layer membrane system were used to determine the penetration of Salicylic Acid (Neubert et al., 1990). Ten mg of Salicylic Acid was applied to a 4.0 cm^2 area in both the experiments using the skin samples and the membrane system, and they were performed four-fold and six-fold, respectively. Using the human skin samples, 20 tape-strippings of the horny layer were removed and assayed for Salicylic Acid content.

The amount of Salicylic Acid from an aqueous (5.0 g cholinsalicylate, 47.5 g PEG 1500, 47.5 g PEG 400) emulsion that penetrated the horny layer after 30 and 60 min was 20.5 and 20.7% of the dose, respectively, while the amount that remained in the emulsion was 12.7 and 10.9%, respectively. After 30 min, the Salicylic Acid content was greatest in tape strippings 1-5 (7-16 µg) and 5-10 (5-8 µg). The same trend was observed after 100 min (7-12 µg in strips 1-5 and 5-9 µg in strips 5-10).

Salicylic Acid in both vaseline and in the Aqueous emulsion were used with the membrane system. With vaseline as the base, 9.0, 6.0, and 5.0% of the dose penetrated into membranes layers 1, 2, and 3, respectively, after 30 min and 10.0, 9.0, and 9.2% penetrated into these layers, respectively, after 60 min. Using the Aqueous emulsion, 21.3, 12.9, and 8.4% of the dose penetrated into layers 1, 2, and 3, respectively, after 30 min and 17.8, 15.8, and 14.9% penetrated into these layers, respectively, after 60 min.

The *in vitro* penetration of Salicylic Acid through human skin (obtained by surgical operation) was compared to that through rodent skin (Harada et al., 1993). Using Franz-type diffusion cells, Salicylic Acid in isotonic buffer, 500 µg/ml, was applied to a 0.785 cm^2 area of human skin from a number of sites and male Wistar and hairless rat and male nude mouse skin.

At pH 4.0, Salicylic Acid penetrated human skin in a "zero-order fashion following a lag time". The penetration rates (µg/h/cm^2) were approximately 18 through scrotum skin (one sample), 2.3 through the cheek (one sample), 2.0 through neck skin (one sample), 1.25 through inguenal area skin (two samples), 0.5 through thigh (three samples) and foot skin (one sample), and <0.5 through lower leg (one sample), breast (five samples), and back skin (one sample); penetration of Salicylic Acid was not detectable through the sole.

The effect of pH on penetration was determined using human breast and neck, hairless rat, Wistar rat, and nude mouse skin at pH 2.0-4.0. Penetration was always greatest at pH 2.0. At pH 2.0, the mean penetration rates through human breast and neck, hairless rat, Wistar rat, and nude mouse skin were 5.97, 10.29, 5.23, 12.41, and 9.77 µg/h/cm^2, respectively. At pH 4.0, these values were 0.37, 1.97, 0.66, 1.03, and 1.60 µg/h/cm^2, respectively. The researchers also examined the effect of age of the skin donor (5 female donors, 38-74 years of age) on penetration using breast skin; no effect was observed. Using human thigh and hairless rat skin, the researchers determined that the stratum corneum was the primary permeability barrier.

The dermis from human mid-abdominal skin was used to determine the *in vitro* absorption of Salicylic Acid in isotonic saline buffer (Singh and Roberts, 1993). Diffusion cells mounted on the skin were used for application. Using four samples, the permeability coefficient was 0.017 cm/h.

Singh and Roberts (1994) examined the penetration of Salicylic Acid across human epidermis isolated from the midabdominal region. Penetration was determined at full and 50% ionization. The permeability coefficients at 100 and 50% ionization were 0.000331 and 0.0152 cm/h, respectively.

In Vivo Human Data

A dose of 4 µg/cm^2 of ^{14}C-Salicylic Acid, 1 µCi, was applied in an open manner to a 13 cm^2 area of the ventral forearm of 17 subjects; urinary excretion was measured for 5 days (Feldmann and Maibach, 1970). Total absorption of Salicylic Acid was 22.78% of the applied dose. The greatest absorption rate, 0.535%/h, was observed 12-24 h after dosing.

Treatment levels (not specified) of Salicylic Acid were applied to large areas of the body of 21 patients with dermatoses, and plasma salicylate concentrations were determined (Schuppli et al., 1972). The average plasma Salicylic Acid concentration was 5.4 mg%, with 15 mg% being the greatest value observed. The average plasma Salicylic Acid value for 22 untreated patients was 3.9 mg%.

Approximately 0.5 g of a salve containing Salicylic Acid was applied to the trunk and extremities of 10 male subjects, and urinary excretion was measured (Panse et al., 1974). The mean amount applied was 9.10 mg/kg. Mean urinary excretion was 0.417, 0.572, and 1.060% of the dose after 12, 24, and 48 h, respectively.

Four patients with active psoriasis (>25% of the body surface involved) were used to determine the dermal absorption of 6% Salicylic Acid in a 60% propylene glycol/19.4% alcohol gel (Taylor and Halprin, 1975). After showering, the patients applied the test material to their entire body surface below the neck, and the treated areas were occluded for 10 h. After the occlusive dressings were removed, the patients showered. This treatment was repeated for a total of five days. Blood samples were taken daily prior to application and 5 and 10 h after application. Twenty-four h urine collections were made for a total of 7 days.

The subjects applied 9.4-22.6 g of the gel daily. The four subjects had total absorptions of 64, 82, 63, and 69%; the patient with the greatest absorption had the most widespread psoriasis, with >90% involvement. A total of 3708, 4998, 5898, and 4104 mg Salicylic Acid per patient was applied, and a total of 2370, 4072, 3740, and 2827 mg salicylate per patient, respectively, was excreted. The urinary metabolites were primarily SUA (41-65% on the days of dosing) and acyl and phenolic glucuronides of Salicylic Acid (32-57% on the days of dosing). The percentage of Salicylic Acid recovered in the urine ranged from 0-14% on the days of dosing. Salicylates were still excreted in the urine on days 6 and 7. The serum salicylate concentration was always <5 mg/100 ml, and the average peak serum concentration was 2.7 mg/100 ml. The serum salicylate concentration peaked within 5 h after application for three of the four patients; salicylate concentrations were low or undetectable 24 h after application. It did not appear that salicylate accumulated during dosing.

The dermal absorption of Salicylic Acid through human skin from two different vehicles was determined (Birmingham et al., 1979). Salicylic Acid, 3% in an aq. solution of 40% polyethylene glycol (PEG) 400 [PEG-8] U.S.P., was applied by immersing the forearm of two subjects in the solution. A hydrophilic ointment containing 10% Salicylic Acid was "evenly spread" over the forearm of four subjects, and the site was occluded. In another two subjects, the skin on the forearm was stripped with adhesive tape prior to application of the ointment. The exposure time for the solution and the ointment was 3 h, after which time the forearms were washed and rinsed. Blood was collected prior to exposure and at hourly intervals for 8 h from an indwelling catheter placed in the opposite forearm.

Salicylic Acid in PEG resulted in minimal systemic absorption, with plasma Salicylic Acid concentrations of <1.0 mg/dl. The researchers stated that the poor-systemic absorption could be "attributable to the formation of a glycol-salicylate complex resulting in a molecule too large to pass the stratum corneum." However, keratolysis was observed within 24 h on the arms of both subjects exposed to Salicylic Acid in PEG.

Application of the Salicylic Acid ointment to intact skin did not produce detectable salicylate in the blood. Although, "appreciable salicylic acid absorption" was observed in the two subjects whose arms were tape-stripped prior to application. In these subjects, the peak salicylate concentration was approximately 8 mg/dl; the calculated absorption rate constant (k_a), elimination rate constant (k_{el}), and $t_{½}$ were 0.189/h, 0.201/h, and 3.450 h, respectively. Using these data, and assuming the 10% Salicylic Acid ointment was applied every 12 h to 30% of a patient's total sur-

face area, plasma Salicylic Acid concentrations would exceed 20 mg/dl after the first application and a steady-state concentration of 30 mg/dl would be obtained after the third application.

The percutaneous absorption of Salicylic Acid in a bath was determined using 15 subjects (Pratzel et al., 1990). The subjects took 20 min baths with 0.33 g/l Salicylic Acid. (The bath preparation contained 25.0 g Salicylic Acid, 5.0 g sodium huminate, and 0.5 g camphor.) Blood was taken at various times for 24 h, and urine was collected for 72 h. The mean plasma Salicylic Acid concentrations for 12 subjects were 10.80, 9.97, 10.47, 9.5, 10.12, and 9.72 ng/ml 1, 2, 4, 6, 8, and 24 h after the bath, respectively. The mean amount of Salicylic Acid excreted in the urine of 14 and 15 subjects was 0.086 and 0.078 mg at 0-24 and 24-48 h, respectively. The mean amount of salicyluric acid excreted in the urine of 15 subjects was 0.92 and 0.72 mg at 0-24 and 24-48 h, respectively. The elimination half-life ($t_{1/2}$) was 30-50 h. The calculated area under the curve (AUC) was 921 h x ng/ml.

The percutaneous absorption of Salicylic Acid from an ointment containing 3% Salicylic Acid and 0.1% diflucortolone-21-valerate (DFV) was determined using a group of six human subjects (Täuber et al., 1993). The subjects were treated twice daily for 8 days with 20 g of the test material; the ointment was applied to the trunk, upper arms, and thighs. The ointment was left in contact with the skin for 22 h/day, and the treated areas were covered with a cotton dressing. The concentration of Salicylic Acid in the plasma was determined from one day prior to until 4 days after dosing. The concentration of Salicylic Acid in the plasma increased during the day; 2-3 µg/ml were present in the morning and 4-7 µg/ml were present in the afternoon. The AUC (0-8 days) was calculated as 30 µg·day/ml.

The relative bioavailability of Salicylic Acid from two different vehicles after repeated dermal application was determined for female human subjects with various skin types (Davis et al., 1997). The test articles, which consisted of 2% Salicylic Acid in either a hydroalcoholic vehicle (63% water/35% ethanol) or a cream (80% water/18% cosmetic excipient mixture), were applied to the faces and necks of the subjects once daily for 16 days. Each application consisted of approximately 1.25-1.50 g of the test material (25-30 mg Salicylic Acid). Nine and 10 subjects with normal skin were dosed with Salicylic Acid in the hydroalcoholic and in the cream vehicle, respectively, nine subjects with acnegic skin were dosed with Salicylic Acid in the hydroalcoholic vehicle, and nine subjects with aged skin were dosed with Salicylic Acid in the cream vehicle. A reference control group of 10 subjects was given 81 mg of acetylsalicylic acid once daily. Blood samples were taken on days 0, 7, and 12, and at a various intervals on day 15. Urine was collected for 24 h on day 15. One subject did not complete the study, and two subjects were excluded from data analysis because of suspected noncompliance (due to "abnormally high baseline concentrations" of salicylates or Salicylic Acid) regarding self-medication.

No skin irritation was observed and no adverse reactions were reported. Steady-state was reached by day 7. Peak plasma Salicylic Acid concentrations were significantly greater, and time to peak occurred earlier, in the groups that received Salicylic Acid in the hydroalcoholic vehicle as compared to those that received it in the cream. The Salicylic Acid terminal exponential $t_{½}$ was significantly shorter in subjects given acetylsalicylic acid orally compared to all groups given Salicylic Acid dermally. When comparing the terminal exponential $t_{½}$ among the subjects dosed with Salicylic Acid, skin type and/or vehicle did not have an effect. AUC Salicylic Acid values were significantly greater in the subjects given Salicylic Acid in the hydroalcoholic vehicle as compared to those given it in the cream. Skin type did not significantly affect any of the parameters.

Six subjects were used to determine the percutaneous absorption of Salicylic Acid (Wester et al., 1998). ^{14}C-Salicylic Acid (0.46 mCi/mg), 39.7 µg/cm^2, in ethanol was spread over a 10 cm^2 area of the ventral forearm for 24 h; the site was not covered. Starting the day of dosing, 24 h urine collections were made for 7 days. The test site was tape stripped 7 days after application. Percutaneous absorption was determined based on urinary ^{14}C-excretion. The mean 7-day urinary excretion of Salicylic Acid was 5.8 ± 4.5% (range of 2.3-13.6%); 53.4% was recovered in the wash and only 0.22% was recovered with tape stripping. The researchers compared the results with those obtained using the isolated perfused porcine skin flap system (IPPSF). A 10 cm^2 area

on five IPPSFs was dosed in manner similar to the human skin. After 8 h, 7.1 and 0.43% of the dose was recovered in the skin and the perfusate, respectively; 16.6 and 48.2% of the dose was recovered in the tape strips and the wash, respectively.

The dermal penetration of Salicylic Acid was determined in normal and barrier-perturbed skin of 16 subjects, nine males and seven females, using microdialysis (Benfeldt et al., 1999). A Latin square design was used, and penetration was determined at the following four sites on the forearm of the subjects: normal skin; skin that had partial removal of the stratum corneum via tape-stripping; skin with irritant dermatitis induced by pretreatment with 1 or 2% sodium lauryl sulfate (SLS) for 24 h; and acetone-treated skin. An equilibration period of 1 h was allowed after insertion of the microdialysis probes, which were inserted 15 min after barrier perturbation. After equilibration, 5 ml of a 5% w/v solution of Salicylic Acid in ethanol was added to the chamber, and perfusion continued for 4 h. With some subjects, a fifth site was used as a control; ethanol was added to the chamber. Drug concentration controls were done by taking a sample of the test solution from each chamber at the start of the study; at the completion of each study, samples were also taken from the chambers of eight subjects and analyzed for Salicylic Acid. Skin thickness and probe depth were measured at the completion of the test using ultrasound scanning.

Salicylic Acid was detectable in all samples from areas to which it had been applied; the concentration increased rapidly up to 70 min. Comparing the AUC from 0-200 min, Salicylic Acid penetration increased 2.2-, 46-, 146-, and 157-fold in acetone-treated, 1% SLS pretreated, 2% SLS pretreated, and tape-stripped skin, respectively, as compared to normal skin. Transepidermal water loss, which was also measured at each site, was 4.3, 9.1, 19.5, 30.1, and 30.6 g/m^2/h at the normal and acetone-treated, 1% SLS-treated, 2% SLS-treated, and tape-stripped sites, respectively. Skin thickness at each of these sites was 1.72, 1.75, 1.85, 2.14, and 1.9 mm, respectively.

An intraregional variation in reactivity to barrier damage was observed; the most proximal location had higher reactivity scores. The sex of the subject had no effect on the penetration of Salicylic Acid. With the vehicle control using five subjects and 10 probes, occasional Salicylic Acid concentrations of 5-10 ng/ml were seen in eight of the probes. In the drug concentration controls, the initial Salicylic Acid concentration of 48.9 mg/ml increased by a mean of 7% over the 4 h.

Ethylhexyl Salicylate

The dermal penetration of Ethylhexyl (Octyl) Salicylate was measured using two different vehicles both *in vivo* and *in vitro*.

In Vitro Human Data

In the *in vitro* study by Treffel and Gabard (1996), skin samples from two women were dermatomed to a thickness of 600 µm. A dose of 2.26 and 2.52 mg/cm^2 of 3% Ethylhexyl (Octyl) Salicylate in the o/w emulsion gel and petroleum jelly, respectively, was applied for 2 min, 30 min, 2 h, or 6 h to a 1.76 cm^2 area of skin in a Franz cell. In the epidermis, 0.94, 2.13, 1.54, and 7.29% of the dose from the o/w emulsion-gel vehicle and 1.81, 0.60, 1.97, and 1.96% of the dose from petroleum jelly was recovered after 2 min, 30 min, 2 h, and 6 h, respectively. None to very little of the dose was recovered from the dermis at any time, and none was detected in the receptor fluid.

In Vivo Human Data

In the *in vivo* study by Treffel and Gabard (1996), 2 mg/cm^2 of 3% Ethylhexyl (Octyl) Salicylate in an o/w emulsion gel and in petroleum jelly were applied to a 100 cm^2 area of the back of four subjects. The sites were wiped 30 min and 2 and 6 h after application, and 15 tape stripping were performed. Sun protection factor (SPF) measurements were performed prior to and 30 min after application; a multiport solar UV simulator was used as the light source.

Maximal concentrations were reached 30 min after application. At this time, approximately 37% of the Ethylhexyl (Octyl) Salicylate in the o/w emulsion gel was found in the stratum corneum in tape strippings 1-5, as compared to approximately 10% of the Ethylhexyl (Octyl) Salicylate in petroleum jelly. The amount found in tape strippings 6-10 and 11-15 was approximately 9 and 4%, respectively, from the o/w emulsion gel and 3 and 1%, respectively, from petroleum jelly. Significantly more Ethylhexyl (Octyl) Salicylate

was absorbed from the o/w emulsion gel vehicle as compared to the petroleum jelly vehicle. The SPF values prior to wiping were 14.2 ± 3.6 and 5.4 ± 1.3 for the emulsion gel and petroleum jelly, respectively. These values decreased by a factor of 2.2 after wiping. Again, the difference between vehicles was significant.

Methyl Salicylate

There are *in vitro* and *in vivo* animal and *in vivo* human data on the the dermal absorption, distribution, metabolism, and excretion of Methyl Salicylate.

In Vitro Animal Data

The *in vitro* percutaneous absorption of Methyl Salicylate was determined using whole skin from the external ears of Landrace pigs (Loveday, 1961). At concentrations of 0.1-0.75 mg/ml, the penetration rate was approximately 0.125-0.6 mg/cm^2/24 h. At a concentration of 1 mg/ml, the pH of the buffer solution did not affect the rate of penetration.

Yano et al. (1991) performed an *in vitro* study using hairless mouse skin to determine the effect of menthol and camphor on the metabolism of Methyl Salicylate to Salicylic Acid. *In vitro* hydrolysis of Methyl Salicylate to Salicylic Acid was linear using skin, liver, and serum enzyme preparations. The formation of Salicylic Acid was inhibited by l-menthol and dl-camphor in a dose-dependent manner. Bis-para-nitrophenyl phosphate, an esterase inhibitor, produced 1000 times stronger inhibition than menthol and camphor.

The percutaneous absorption and metabolism of radioactive Methyl Salicylate was determined after application to viable and non-viable skin from male and female hairless guinea pigs in an *in vitro* study using flow-through diffusion cells (Boehnlein et al., 1994). Groups of three animals and three to four repetitions per animal, were used. Methyl Salicylate in acetone was applied to the skin at a dose of 5 µg/cm^2. After 24 h, the surface was thoroughly washed to remove unabsorbed material. It was found that Methyl Salicylate did not spontaneously degrade in the receptor fluid, and that the metabolism that occurred took place during absorption through the skin and not as a result of contact with the receptor fluid.

No significant difference was observed in the percutaneous absorption of Methyl Salicylate through viable and non-viable skin from male or female hairless guinea pigs. The percutaneous absorption, as a percentage of the applied dose absorbed in 24 h, was 55 ± 6 and 56 ±16 for male and females, respectively, through viable skin and 47 ± 2 and 50 ± 20 for males and females, respectively, through non-viable skin. Absorption was rapid, with greater than 75% of the absorbed compound found in the receptor fluid collected in the first 6 h.

Unlike absorption, the metabolism of Methyl Salicylate was significantly different in skin from males and females as well as in viable and non-viable skin. In viable skin, esterase activity was observed, and Salicylic Acid was then metabolized by glycine conjugation to SUA. In non-viable skin, only esterase activity was observed. In viable skin of male animals, the metabolism of Methyl Salicylate, as a percentage of absorbed dose metabolized, was 36 ± 6 and 21 ± 5 to Salicylic Acid and SUA, respectively, for a total of 56 ± 5% of the absorbed dose metabolized. In viable skin of female animals, 12 ± 2 and 12 ± 4% was metabolized to Salicylic Acid and SUA, respectively, with a total of 25 ± 3% of the absorbed dose metabolized. In non-viable skin from male and female animals, 38 ± 5 and 13 ± 3% of the absorbed dose, respectively, was metabolized to Salicylic Acid. The formation of Salicylic Acid in the skin from males represented 34% of the absorbed radioisotope, as compared to 5% in skin from females. In examining the time course of metabolism, the extent of metabolism in male and female guinea pig skin was significantly different only at the 6-h interval.

The percutaneous absorption of Methyl Salicylate through intact hairless mouse skin was determined *in vitro* using a glass flow-through diffusion cell system (Higo et al., 1995). A 0.95 cm^2 area of skin was exposed to 1% w/v Methyl Salicylate, pH 4.0. The penetration flux decreased 4 h after application. Approximately 17 µmol Salicylic Acid penetrated after 10 h. When a lower concentration was tested, a lower flux through the skin was observed, and more of the Methyl Salicylate was metabolized. Pretreatment of skin with l-menthol for 14 h prior to excision inhibited the metabolism of Methyl Salicylate to Salicylic Acid, but it did not

significantly affect penetration.

In Vivo Animal Data

The depth of penetration following topical application of Methyl Salicylate was determined using male Wistar rats (Megwa et al., 1995). Five preparations containing 10-28.3% Methyl Salicylate (Salicylic Acid equiv. of 18.9 mg/cm^2) were each applied to a 9.625 cm^2 area of depilated abdominal skin. The untreated contralateral side was used as the control. After 2 h, the formulations were removed using a spatula and blood samples were taken. The animals were then killed and tissue samples (skin, s.c., top muscle, deep muscle, and fat) were sequentially removed from below the test and control sites.

Methyl Salicylate was primarily converted to Salicylic Acid during transport through the skin. The plasma Salicylic Acid concentration, which ranged from approximately 200-325 µg/g, was greater than the plasma Methyl Salicylate concentration, which ranged from approximately 25-50 µg/g, with application of all formulations. Salicylate appeared to directly penetrate to the s.c. tissue or top muscle underlying the treated area. Salicylate concentrations in the deeper tissues underlying the test site and on the contralateral side were similar, suggesting that the salicylate present in these tissues was due to systemic blood supply. Similar results were seen in preparations that contained 10% TEA-Salicylate in addition to Methyl Salicylate.

The percutaneous absorption of ^{14}C-Methyl Salicylate from medicated plaster (8.47 µCi [3.54 mg] in 10 mm x 10 mm plaster) was determined using hairless HRS/J (hr) mice (Maruta et al., 1977). The plasters, which were covered, were applied for 1-48 h; the animals were killed at the termination of dosing. "High levels of radioactivity" were found in the skin at the test site 1 h after application; the amount peaked at 4 h and then declined. Very little radioactivity was seen at 48 h. "Slight radioactivity" was detected in skin adjacent to the test site at 2 and 4 h. Serum radioactivity peaked at 2 h at 15 µg/ml salicylates. Cumulative urinary excretion of the radioactivity was 27.2, 33.5, and 39.3% of the dose after 12, 24, and 48 h, respectively.

Female hairless HRS/J (hr) mice were used to determine the dermal penetration and metabolism of, and the effect of l-menthol and dl-camphor on, Methyl Salicylate (Yano et al., 1991). A 2 x 2 cm plaster sheet containing 5.2 mg Methyl Salicylate, with or without 4.8 mg l-menthol and 1.0 mg dl-camphor, was applied to the dorsal skin of each animal for 1, 3, or 6 h. The animals were then killed and the skin removed, rinsed, and minced. In skin not exposed to menthol and camphor, the dermal concentrations of Methyl Salicylate and Salicylic Acid after 1 h were 0.64 and 0.49 µmol/g, respectively; these values decreased to 0.29 and 0.22 µmol/g after 6 h. Application of menthol and camphor increased the dermal concentrations of Methyl Salicylate and Salicylic Acid. After 1 h, these values were 1.79 and 0.39 µmol/g, respectively.

Male Sprague-Dawley rats were used to determine the effect of pH on dermal absorption of Methyl Salicylate (Siddiqi and Ritschel, 1972). The tails of the animals were immersed in a Methyl Salicylate solution containing 5% ethanol that had a pH of 2, 3, 6, or 8. At pH 2, 3, 6, and 8 the total amount absorbed was 1.56, 0.76, 1.77, and 1.57 µg/mm^2/h, respectively, the k_a was 3.5439, 0.7421, 1.2059, and 2.2173/h, respectively, and the α was 0.645×10^{-6}, 0.645×10^{-5}, 0.645×10^{-2}, and 0.641%, respectively.

In Vivo Human Data

The dermal absorption of 20% Methyl Salicylate from three different vehicles was determined in male subjects by measuring urinary excretion (Beutner et al., 1943). The three ointments consisted of 20% Methyl Salicylate and 80% anhydrous lanolin (ointment 1), 60% anhydrous lanolin and 20% menthol (ointment 2), or 60% of a special aq. base of 35% glycerin monostearate, 4.2% phenolic resin, 3.5% acacia, 28% water, 28% alcohol, and 1.3% glycerin and 20% menthol (ointment 3). Each subject applied and rubbed in a total of 10 g of ointment to the skin of the chest, abdomen, and thigh. Urine was collected.

A qualitative determination using eight subjects showed that salicylate was excreted within 2 h for 2 subjects, 12 h in five subjects, and >12 h in one subject. The mean salicylate excreted by the five, 22, and 15 subjects that applied ointments 1, 2, and 3 was 41.6, 55.1, and 47.5 mg, respectively. Eight subjects who had "better cutaneous absorption than the average" ("dark-complexioned individuals apparently [had] a

higher absorption ability than blonds") were used to compare the excretion of salicylate following dermal inunction of ointments 1, 2, and 3; 64.6, 101.3, and 103.1 mg salicylate, respectively, were excreted. Menthol appeared to enhance absorption.

Methyl Salicylate was applied to the forearms of subjects under a 1 x 5 x 10 cm plastic cell using hydrous and anhydrous conditions (Wurster and Kramer, 1961). For the hydrous condition, a 5 x 10 cm sponge was filled with 6 ml Methyl Salicylate and 3 ml distilled water, and for the anhydrous condition, the cell was filled with magnesium perchlorate and the sponge with 6 ml Methyl Salicylate without water. Urine samples were taken every 2 h during exposure. The cell was removed after 16 h, and the test site was washed. The urinary excretion rate for Methyl Salicylate was 8.6 and 2.7 mol/100 cm^2/h with hydrous and anhydrous exposure, respectively. In both cases, steady-state was reached at approximately 6 h.

Wurster and Kramer (1961) also determined the absorption of Methyl Salicylate through defatted and nondefatted skin. For the test using defatted skin, the arms of each subject were immersed in ethyl ether for 1 min. For both tests, "an excess of Methyl Salicylate" was applied on a 100 cm^2 area of the forearm for 2 h. The test area was washed. Urine was collected every 2 h until negative for salicylate. Defatting of the skin decreased total salicylate absorption by 27%.

The dermal absorption of Methyl Salicylate from medicated plaster (containing 35.0 mg Methyl Salicylate/sheet) was determined using groups of six subjects (Maruta et al., 1977). One group received a single covered application to the back of 10 sheets of the plaster to the back, while the second group received repeated covered 12 h applications for 6 days of 10 sheets, with a 12 h non-treatment period in between. With the single application, blood samples were taken 4-48 h after application initiation and urine was collected for 48 h. With multiple applications, blood samples were taken immediately before the third and fifth application and 12 and 36 h after removal of the final application.

With the single application, serum free Salicylic Acid peaked at 8 h after dose initiation at approximately 4 µg/ml; no free Salicylic Acid was determined in the serum at 48 h. Greatest total salicylate concentration, 12.5 µg/ml, occurred at 12 h. The cumulative total salicylates excreted in the urine was approximately 37% of the applied dose; 70% of this amount was excreted during the application period. With repeated applications, a trace to no free Salicylic Acid or total salicylates was found in the serum.

Five subjects were used to determine the dermal permeability and plasma uptake of five products containing 12-50% Methyl Salicylate (Roberts et al., 1982). Five g of each product was applied to a 50 cm^2 area on the forearm of each subject in a Latin Square design; a small portion of the product was rubbed into the area and the remaining product was spread over the site. The test site was occluded for 10 h, after which time it was washed. There was a 1-wk period between product applications. One of the products, which contained 25% Methyl Salicylate, was also applied to the abdomen, instep, heel, and plantar region of four subjects following the same protocol. Methyl Salicylate absorption and excretion was estimated from the total urinary excretion of salicylate. Urine was collected at various intervals for up to 48 h after application.

When applied to the forearm, skin permeability coefficients were similar for each product and ranged from 1.0 ± 0.4 to 1.9 ± 0.5 cm/h. The amount of salicylate absorbed from each product after application to the forearm ranged from 12-20%, and the estimated steady-state salicylate concentration ranged from 2.5-7.6 mg/l. The skin permeability coefficient, the percentage of salicylate absorbed, and the cumulative urinary salicylate recovery was greatest upon application to the abdomen, followed by the forearm, instep, heel, and the plantar area. Pain and redness were experienced by all test subjects at all sites of application, but the amount of pain associated with application to each site as reported by the subjects was greatest at those sites with the greatest absorption.

The dermal penetration of a product containing 1% w/w Methyl Salicylate that was applied as a metered aerosol was determined in human subjects (Collins et al., 1984). The product also contained 5% w/w of each ethyl and 2-hydroxyethyl salicylate. The product was sprayed onto the forearms of the subjects, but was not massaged. Platelet aggregation and venous blood ethyl and Methyl Salicylate concentrations were

measured using six subjects, two males and four females, and venous blood oxygen was measured using two subjects.

Methyl Salicylate was absorbed faster than ethyl salicylate, but the concentration of ethyl salicylate in blood was greater. A relatively high salicylate concentration was found for up to 1 h after dosing in blood drawn from the treated arm; the amount of Methyl Salicylate found in the plasma peaked at approximately 20 min after dosing. A small amount of salicylates was detectable for only 20 min in blood drawn from the untreated arm. Platelets were resistant to arachidonic acid-induced clumping for approximately 15 min after application; this effect was not observed in blood drawn from the untreated arm. Venous blood oxygen increased, peaking between 30-40 min and then declining, in blood drawn from the treated arm; again, this effect was not seen in blood drawn from the untreated arm.

The effect of exercise and/or heat on the percutaneous absorption of Methyl Salicylate was determined using six male subjects (Danon et al., 1986). Five g of Methyl Salicylate were applied to the back and chest, and the subjects were exposed to heat, exercise, or both for 6 h. Blood samples were taken at 0, 1, 2, 3, and 5 h and urine was collected hourly for 8 h. Exercise and/or heat increased plasma total salicylate concentrations and urinary SUA, indicating increased systemic salicylate availability. Plasma salicylate peaked at 2 h under all conditions; values at 1, 3, and 5 h were significantly increased with heat exposure compared to controls. The AUC_{0-5} was significantly increased under test compared to control conditions. The urinary metabolic profile was similar under all test and control conditions; SUA comprised 95% of the urinary metabolites. However, heat and/or exercise resulted in an increase in the excretion of SUA; 2.6% of the applied dose was excreted following heat and exercise as compared to 1.0% under control conditions.

The percutaneous absorption of Methyl Salicylate in a bath was determined using 10 subjects (Pratzel et al., 1990). The subjects took 20 min baths with 0.03 g/l Methyl Salicylate. (The bath preparation contained 15.0 g Methyl Salicylate, 1.5 g Siberian spruce-needle oil, 4.0 g thyme oil, and 3.0 g camphor.) Blood was taken at various times for 24 h, and urine was collected for 72 h. The mean plasma Salicylic Acid concentrations for 20 and 10 subjects were 452.6 and 116.6 ng/ml 1 and 6 h after the bath, respectively. For one subject, the 2, 4, 8, and 24 h values were 308, 171, 63, and 41 ng/ml, respectively. The mean amount of salicyluric acid excreted in the urine was 5.08, 0.71, and 0.97 mg at 0-12, 12-24, and 24-48 h, respectively. The elimination $t_{1/2}$ was 2.4-4 h. The calculated AUC was 1000-3900 h x ng/ml.

Twelve subjects, six men and six women, were used to determine rate and extent of absorption following dermal application of an ointment containing 12.5% Methyl Salicylate (Morra et al., 1996). Five g of the ointment (equiv. to 567 mg salicylate) was applied twice daily for 4 days to a 10 cm^2 area on the anterior aspect of the thigh under a non-occlusive patch. Blood samples were taken on days 1 and 4 just prior to dosing and at various intervals up to 24 h after the first daily application. Twenty-four h urine collections were made during the entire study.

No unchanged Methyl Salicylate was detected in the serum samples. (The limit of detection was 0.3 mg/l.) Serum Salicylic Acid concentrations ranged from 0.3-0.9 mg/l within the 1 h of the first application and 2-6 mg/l on day 4. The mean serum pharmacokinetic values are summarized in Table 5.

Unchanged Methyl Salicylate was not detected in the urine. (The limit of detection was 1 mg/l.) Unchanged Salicylic Acid and SUA were detected in all urine samples at concentrations up to 15.6 and 491.9 mg/l, respectively. Glucuronides were also present. The total Salicylic Acid recovered on days 1, 2, 3, and 4 was 175.2, 249.0, 254.1, and 251.4 mg, respectively, and the percent recovered for these days was 15.5, 22.0, 22.4, and 22.2%, respectively. The difference in recovery between day 1 and days 2, 3, and 4 was significant.

Sodium Salicylate

There are *in vivo* animal and *in vitro* human data on the dermal absorption, distribution, metabolism, and excretion of Sodium Salicylate.

In Vivo Animal Data

The percutaneous absorption of Sodium

Table 5. Mean Salicylic Acid Serum Pharmacokinetic Values after Dermal Application of Methyl Salicylate (Morra, et al., 1996)

Pharmacokinetic parameters	Salicylic Acid concentration	
	DAY 1	DAY 4
Minimum concentration (C_{min}) (mg/l)		
0 h	0.00	2.0 ± 1.1
12 h	1.2 ± 0.7	1.7 ± 1.1*
24 h	1.5 ± 0.8	1.9 ± 1.0
Maximum concentration (C_{max}) (mg/l)	1.7 ± 0.7	3.9 ± 1.2*
Time to C_{max} (h)	6.0 ± 2.0	4.4 ± 1.3
AUC_{0-12} (mg·h/l)	15.3 ± 6.6	35.8 ± 11.8*
Apparent oral clearance (l/h)	3.89 ± 1.32	
Apparent oral volume of distribution (l)	20.28 ± 6.15	
k_{el} (/h)	0.1955 ± 0.0441	
k_a (/h)	0.1608 ±0.0441	0.2803 ± 0.2489*

*significantly different from day 1 value

Salicylate from four different vehicles was determined using groups of 10 New Zealand white rabbits (Stolar et al., 1960). Sodium Salicylate, 6.95%, was added to the oleaginous base petrolatum USP XV, the hydrophilic base petrolatum USP XV with water, the o/w base hydrophilic ointment USP XV, and the water-soluble base PEG ointment USP XV. The hair on the back of each animal was shaved, and 7.5 g of each ointment was applied to a 6.35 x 12.7 cm area under an occlusive patch for 9 h. Blood samples were taken hourly. The greatest absorption was observed from the hydrophilic ointment; peak absorption was approximately 4.6 mg% at 5 h. The peak absorption concentration with petrolatum and hydrophilic petrolatum with water were approximately 1.0 and 0.4 mg% at 6 and 5 h, respectively. Negligible absorption was seen with the PEG ointment.

New Zealand white rabbits were used to determine the absorption of 11.6% Sodium Salicylate from hydrophilic ointment and hydrophilic petrolatum bases, with and without DMSO (Stelzer et al., 1968). (Protocol described previously.) Blood salicylate concentrations peaked at 8 h with all formulations. The peak values from hydrophilic ointment were 4.03 and 1.38 mg% without and with DMSO, respectively, and from hydrophilic petrolatum were 4.03 and 1.38 mg% without and with DMSO, respectively.

The percutaneous absorption of Sodium Salicylate, with and without DMSO and with and without nonionic surfactants, was determined using New Zealand white rabbits (Shen et al., 1976). (Protocol described previously.) The approximate peak blood salicylate values and times are summarized in Table 6.

Using guinea pigs, Yankell (1972) determined whether lateral diffusion occurred with the application of ^{14}C-Sodium Salicylate (equiv. to 3% Salicylic Acid) in water; absorption was compared to that of 3% ^{14}C-Salicylic Acid in 75% ethanol. Lateral diffusion did not occur; <2% of either applied dose was found in sites adjacent to the test site.

In Vitro Human Data

The absorption of 5% Sodium Salicylate from five

Table 6. Peak Blood Salicylate Values with Sodium Salicylate in Various Formulations

Test Article	Peak Value (mg%)	Time of Peak Value (h)
Salicylic Acid (SA)	2.5	8
SA + DMSO	1	8
SA + DMSO + Poloxamer 182	3.5	4
SA + DMSO + Poloxamer 184	2	5
SA + DMSO + Poloxamer 231	2.75	3
SA + DMSO + Oleth -2	2.75	5
SA + DMSO + Oleth-20	2	5
SA + DMSO + Laureth-4	3	8
SA + DMSO + Sorbitan Laurate	7	6
SA + DMSO + Sorbitan Palmitate	4	6
SA + DMSO + Sorbitan Trioleate	3	4
SA + DMSO + Polysorbate 20	2.25	7
SA + DMSO + Polysorbate 40	2	8
SA + DMSO + Polysorbate 60	2.25	8
SA + DMSO + PEG-8 Stearate	2	8

different vehicles was determined *in vitro* using seven samples of human leg and/or breast skin (Flesch et al., 1955). No penetration was observed with a petrolatum, carbowax, lanolin, Plastibase®, or Hydrophlic Plastibase® (Squibb) vehicle after 24 h of incubation.

The horny layer of excised human skin and a three-layer membrane system were used to determine the penetration of Sodium Salicylate (Neubert et al., 1990). (Protocol described previously.) The amount of Sodium Salicylate from a Aqueous emulsion that penetrated the horny layer after 30 and 60 min was 19.0 and 23.2% of the dose, respectively, while the amount that remained in the emulsion was 26.6 and 24.1%, respectively. After 30 min, the Sodium Salicylate content was greatest in tape strippings 1-5 (5-27 µg). After 100 min, 5-28 µg was found in strips 1-7. Sodium Salicylate in the Aqueous emulsion was used with the membrane system. After 30 min, 20.3, 6.6, and 3.1% of the dose penetrated into layers 1, 2, and 3, respectively, and after 60 min, 26.0, 9.5, and 5.5% of the dose penetrated into these layers, respectively.

TEA-Salicylate

There are *in vivo* animal and human data on the dermal absorption, distribution, metabolism, and excretion of TEA-Salicylate.

In Vivo Animal Data

Groups of eight rabbits were used to determine the dermal absorption of TEA-Salicylate (Panse et al., 1974). Patches containing 5 g of a TEA-Salicylate salve (36.2 mmol/100 g) were applied for 6 h; urinary excretion of Salicylic Acid was measured. Approximately 4.01 and 14.59% of the dose was excreted in the urine after 24 and 48 h, respectively.

Five male Beagle dogs were used in a study in which 10 g of a TEA ^{14}C-Salicylate cream (specific activity 140 dpm/µg of ^{14}C-salicylate, 2.77 mM = 24.3 µCi, specific activity 8.77 µCi/mM) was massaged into the shaved right knee of each animal, and dermal absorption was measured (Rabinowitz et al., 1982). Blood and urine samples were taken 30 or 60 min after application, and tissue samples were taken at the point of application. The ^{14}C-salicylate concentrations in skin at the application site, muscle, fascia,

tendon, ligament, cartilage, bone marrow, bone, synovium, synovial fluid, blood, and urine after 60 min were 312.2, 38.20, 16.40, 3.00, 2.00, 1.62, 1.05, 1.00, 0.74, 0.80, 0.22, and 0.16 µg/ml, respectively. At 30 min, the concentration in the blood was 2.60 µg/ml.

The dermal penetration of TEA-Salicylate was determined using six female Yorkshire swine (Baldwin et al., 1984). A hydrophilic cream, 1.5 g, containing 10% (w/w) TEA-^{14}C-Salicylate (Salicylic Acid equiv. of 72 mg) was applied to a 100 cm^2 shaved area of the biceps femoris of each animal. In four animals, half the test site was washed 30 min after dosing and muscle and fat were removed. This procedure was repeated at 2 h. Blood samples were taken both times. In the remaining two animals, blood samples were taken from shallow incisions 10, 20, and 30 min after dosing.
One non-dose related death occurred. Two h after dosing, 7.9% of the dose remained on the skin and 9.3% remained in the skin tissue. At least 82% of the dose was absorbed in 2 h. Thirty min after dosing, 150.9-724.5 ng/g of muscle tissue (expressed as free Salicylic Acid equivalents) was recovered in the treated muscle and 31.6-56.4 ng/g of blood were recovered in the blood of four animals. At 2 h, 313.5-582.3 ng/g were recovered in the treated muscle and 38.7-84.5 ng/g were recovered in the blood of three animals. In the contralateral muscle (control), only 0-28.7 and 8.6-55.2 ng/g were recovered at 30 min and 2 h, respectively. A much greater amount of salicylate was found in the treated muscle as compared to the control. Little ^{14}C was excreted in the urine; 0.14 and 0.45% of the dose was excreted 30 min and 2 h after dosing, respectively. The ^{14}C recovered in blood from shallow incisions from two animals 10, 20, and 30 min after dosing was equivalent to 15.8, 6.2, and 5.3 µg salicylate/g.

Rabinowitz and Baker (1984) performed studies using male and female Beagle dogs in which radioactive TEA-Salicylate ointment was applied to the shaved knees of the animals, and the penetration was then determined. In one study using five male and 10 female animals, 10 g of radioactive 10% TEA-Salicylate ointment was massaged into a 100 cm^2 area. Tissue samples were taken after 60 min. The average ^{14}C-salicylate concentration in the skin at the application site, fascia, muscle, cartilage, fat pad, tendon, synovial fluid, meniscus, ligament, and serum of the male animals was 50.898, 5.188, 1.847, 1.804, 0.833, 0.579, 0.536, 0.413, 0.253, and 0.004 µmol/g, respectively; for the female animals, these values were 32.644, 3.471, 0.644, 0.507, 0.398, 0.608, 1.434, 0.645, 0.224, and 0.013 µmol/g, respectively. No significant difference in absorption was observed between males and females.

The researchers then examined the effect of varying the amount of radioactive TEA-Salicylate while keeping the weight applied constant; all tissues were examined 60 min after application. Creams containing 5, 1, and 0.1 g radioactive TEA-Salicylate ointment, brought to a weight of 10 g using cold cream, were applied to the knees of 3, 2, and 1 animals and the results were compared with the combined averages of the 15 animals dosed with 10 g radioactive ointment. The amount of recovered ^{14}C-salicylate decreased proportionately.

Rabinowitz and Baker (1984) also applied ^{3}H-(G)-TEA 7-^{14}C-Salicylate to the shaved knees of dogs and determined the concentrations of each radioactive moiety. The concentrations of ^{3}H-TEA recovered in the skin at the application site, fascia, muscle, fat pad, synovial fluid, and serum were 23.695, 2.112, 0.528, 0.300, 0.039, and 0.001 µmol/g, respectively. The concentrations of ^{14}C-salicylate found at these sites were 34.427, 2.655, 1.199, 0.398, 0.061, and 0.002 µmol/g, respectively.

In Vivo Human Data

Six male subjects with seropositive, adult-onset rheumatoid arthritis were used in a study in which 10 g of a TEA ^{14}C-Salicylate cream was massaged into a 25-30 cm^2 area of the skin over one knee, and dermal absorption was measured (Rabinowitz et al., 1982). Blood and urine samples were obtained prior to and 1 or 2 h after application. Synovial fluid aspiration was also performed. The ^{14}C-salicylate concentrations in synovial fluid, blood, and urine were 0.16, 0.03, and 0.02 µg/ml, respectively, at 1 h and 0.25, 0.08, and 0.18 µg/ml, respectively, at 2 h.

Ten hospitalized male patients with classical or definite rheumatoid arthritis, four of which were restricted to bedrest, participated in a study designed to determine the absorption of dermally

applied radioactive 10% TEA-Salicylate ointment (Rabinowitz and Baker, 1984). The ointment was massaged in for 60 min and the skin was then wiped. A synovial fluid aspiration procedure was performed at a site that was not in contact with the TEA-Salicylate ointment. The mean ^{14}C-salicylate concentrations in the synovial fluid, blood, and urine of the six patients not confined to bedrest were 0.0011, 0.0002, and 0.0001 µmol/g, respectively; in the four patients confined to bedrest, these values were 0.0014, 0.0011, and 0.0020 µmol/g. The blood and urine concentrations were significantly different for the two groups of patients.

Twelve subjects, six men and six women, were used to determine the rate and extent of absorption following dermal application of a cream containing 10% TEA-Salicylate (Morra et al., 1996). Five g of the ointment (equiv. to 241 mg salicylate) was applied twice, with 12 h between applications, to a 10 cm^2 area on the anterior aspect of the thigh under a non-occlusive patch. Blood samples were taken just prior to dosing and at various intervals up to 24 h after the first application. Urine was collected for 24 h, starting just prior to the first application. No unchanged TEA-Salicylate or Salicylic Acid was detected in the serum. (The limit of detection was 0.3 mg/l.) The amount of unchanged Salicylic Acid and SUA found in the urine was 1.8 and 9.1 mg, respectively; the Salicylic Acid and SUA concentrations were often below the limit of detections (1 mg/l.) The total Salicylic Acid and percent recovered in the urine was 6.9 mg and 1.4%, respectively.

The dermal absorption, distribution, metabolism and excretion studies described above are summarized in Table 8a at the end of this section.

ORAL ROUTE OF ADMINISTRATION

Salicylic Acid

There are animal and human data on the absorption, distribution, metabolism, and excretion of Salicylic Acid given orally.

Animal Data

Tanaka et al. (1973a) determined the Salicylic Acid concentration in maternal organs and in the fetuses. Five gravid Wistar rats were fed a diet containing 0.2% Salicylic Acid on days 8-14 of gestation. The animals were killed on the last day of dosing. The greatest concentration of Salicylic Acid was in the serum (115.96 µg/ml) and the lowest was in the brain (4.14 µg/g). All other examined organs, including the placenta, had similar concentrations (21.68 - 35.23 µg/g) with the exception of the kidneys, which had a relatively high concentration (60.89 µg/g). Fetal and amniotic fluid concentrations were relatively lower than those observed in maternal organs (13.86 µg/g in the fetus and 12.35 µg/ml in the amniotic fluid).

Tanaka et al. (1973b) determined the Salicylic Acid concentration in maternal organs and in fetuses. Five gravid Wistar rats were given 150 mg/kg Salicylic Acid orally once daily on days 8-14 of gestation or given one dose on day 14 of gestation. The animals were killed 3 h after the final dose. After both single and multiple doses, the greatest concentration of Salicylic Acid was in the serum (246.56 and 221.28 µg/ml, respectively) and the lowest was in the brain (23.82 and 24.86 µg/g, respectively). All other examined organs, including the placenta, had similar concentrations (63.13 - 88.5 µg/g with a single dose; 68.57-85.62 µg/g with multiple doses) with the exception of the kidneys, which had relatively high concentrations (121.18 and 128.47 µg/g with single and multiple doses, respectively). Fetal and amniotic fluid concentrations were relatively lower than those observed in maternal organs (55.83 and 62.48 µg/g in the fetus after single and multiple doses, respectively, and 39.41 and 62.29 µg/ml in the amniotic fluid after single and multiple doses, respectively).

The effect of age and dose on the metabolism and distribution of Salicylic Acid was determined using male Fischer 344 rats (McMahon et al., 1990). A single dose of 5, 50, or 500 mg/kg 7-^{14}C-Salicylic Acid (10 µCi/kg) in corn oil/ethanol (4:1) was given to 3, 12, and 25 mos old animals. Urine and feces were collected for 96 h, after which time the animals were killed. All of the 3 mos old animals dosed with 500 mg/kg Salicylic Acid died and two of the 25 mos old animals were killed at 48 h due to the toxic effects.

Almost all the radioactivity was excreted in the urine. At 5 mg/kg, urinary excretion was complete by 24 h in 3 and 25 mos old animals and by 48 h in 12 mos old animals. At 50 mg/kg, urinary excretion was complete in all groups at

48 h; excretion was significantly decreased in 25 mos animals compared to 3 mos animals at 6, 12, and 24 h. Within each age group, an increase in the dose resulted in an increase in the time for urinary elimination. Fecal excretion of radioactivity at 50 mg/kg was significantly decreased in the 25 mos old animals compared to the other groups; no difference was observed at 5 mg/kg. The urinary metabolite profile was affected by both age and dose.

The permeability of Salicylic Acid through the oral mucosa of male golden hamsters was also investigated by Kurosaki et al. (1991). A thin film dosage form of Salicylic Acid was prepared by drying a viscous solution of Salicylic Acid in ethanol, isotonic buffer solution (pH 3.0), and polyethylene glycol to yield an apparent content of Salicylic Acid of 43.3 µmol/cm^2. Aluminum foil was used as a backing for this film and one piece of the film (8.5 µmol Salicylic Acid/piece) was placed on each of four oral mucosae: sublingual mucosa, dorsum of the tongue, ventral surface of the tongue, and cheek pouch mucosa.

The plasma C_{max} occurred at 45, 60, 120 and 180 min in the sublingual mucosa, ventral surface of the tongue, cheek pouch mucosa, and the dorsum of the tongue, respectively. The C_{max} of the sublingual mucosa (~11.5 nmol/ml) was approximately 4.5 times greater than that in the dorsum of the tongue (~2.5 nmol/ml). Absorption was greatest where the stratum corneum was the thinnest. The authors stated that the finding that the AUC and stratum corneum thickness, but not whole epithelium, are inversely proportional suggests that the stratum corneum is the principal barrier.

Human Data

Four male patients (49, 60, 63, and 77 years of age) were orally given Salicylic Acid as either the free acid in capsules or as the sodium salt in aq. solution, but the concentration and total dose were not given (Alpen et al., 1951). Urine was collected for 24-36 h. The urinary pH ranged from 5.0-6.7 for three of the patients and was 8.5 for the fourth patient. The amount of free Salicylic Acid recovered was 10-85%, of salicyluric acid was 0-50%, of gentisic acid was ≤1%, and of glycuronate conjugates was 12-30% (–OH conjugate) and 0-10% (–COOH conjugate). The total amount recovered in the urine was 85-95% of the dose.

Six female subjects ingested a tablet containing 66 µmol Salicylic Acid (Janssen et al., 1996). The mean recovery of salicylate in the urine over a 24 h period was 80%.

The presence of Salicylic Acid in semen following oral administration of acetylsalicylic acid (aspirin) was determined using seven male subjects (Kershaw et al., 1987). Fasted subjects were given three 325 mg tablets of aspirin. The t_{max} in plasma was 2.5 h and C_{max} was 49 µg/ml, the k_a - and k_{el} were 0.64 and 0.27/h, respectively, and the AUC was 357 h·µg/ml. Elimination of salicylate became log-linear between 6 and 9 h when the amount of salicylate in the body was 200-400 mg (aspirin equiv.). The harmonic mean terminal $t_{½}$ of salicylate was 2.6 h. Equilibration of salicylate between plasma and semen was rapid and independent of Salicylic Acid concentration. The mean concentration ratio (x100) of Salicylic Acid (semen/plasma) was 14.6. The ratio of the salicylate concentration in plasma and semen was independent of the salicylate concentration in the plasma.

Magnesium Salicylate

There are animal and human data on the absorption, distribution, metabolism, and excretion of Magnesium Salicylate given orally.

Animal Data

The bioavailability of Magnesium Salicylate was determined using four female beagle-type mongrel dogs (Alam et al., 1981). Using a 4 x 4 Latin square design with a 1 wk washout period, the animals were dosed with 650 mg Magnesium Salicylate in two different tablet forms, one with a gelatin binder (tablet A) and one with a pregelatinized starch binder (tablet B), or as an aqueous solution (concentration not stated), and 325 mg of aspirin. The fasted animals were given 200 ml water 30 min prior to dosing and 25 ml water immediately following dosing. Blood samples were taken at various intervals at 0-12 h.

No significant differences were observed between administration of Magnesium Salicylate in tablet or solution form. For tablet A, tablet B, the solution, and aspirin, the following pharmacokinetic parameters were determined: C_{max} - 119 ± 7.9,

119 ± 8.9, 117 ± 14.2, and 117 ± 0.2 µg/ml, respectively; t_{max} - 1.6 ± 0.4, 1.2 ± 0.2, 1.0 ± 0.2, and 2.9 ± 0.7 h, respectively; k_a - 3.7 ± 2.1, 3.4 ± 0.9, 4.5 ± 0.8, and 1.2 ± 0.5 h^{-1}, respectively; $t_{½}$ - 8.4 ± 1.1, 6.5 ± 0.8, 8.0 ± 1.1, and 5.4 ± 1.8 h, respectively. The k_{el}, AUC_{0-12}, $AUC_{0-\infty}$, and bioavailability were not different for any of the four.

Human Data

Eighteen fasted male subjects were given a single oral dose of Magnesium Salicylate (equiv. to 481 mg Salicylic Acid) with 240 ml of water, and blood and urine were collected at various intervals for 16 and 24 h after dosing (Mason, 1980). Plasma salicylate and urine salicylurate concentrations were determined. The greatest plasma salicylate concentration, 36.5 µg/ml, was observed 1.5 h after dosing. The AUC_{16} and AUC_{∞} were 223 and 225 µg·h/ml, respectively, and the apparent elimination $t_{1/2}$ was 2.01 h. The plasma C_{max} and the plasma t_{max} were 1.44 µg/ml and 1.44 h, respectively. The greatest urine salicylurate concentration, 393 mg, occurred during the 0-12 h time interval, and the percentage of the dose of salicylate excreted as salicylurate in 24 h was 68.4%.

Methyl Salicylate

There are animal and human data on the absorption, distribution, metabolism, and excretion of Methyl Salicylate given orally.

Animal Data

Groups of 10 rats were dosed orally with Methyl Salicylate in 2% methylcellulose (equiv. to 500 mg/kg Salicylic Acid), and the amount of total salicylate in the plasma and in brain homogenate was determined (Davison et al., 1961). After 20 min, 217 and 8 mg/l free salicylate were found in the plasma and brain, respectively. After 60 min, these values were 278 and 42 mg/l, respectively. Methyl Salicylate values were negligible.

Human Data

Six fasted human subjects, four males and two females, ingested 0.42 ml Methyl Salicylate, and blood samples were taken after 15 and 90 min to determine plasma salicylate values (Davison et al., 1961). After 15 min, the mean Methyl and free salicylate values were 4.9 and 7.9 mg/l, respectively. After 90 min, these values were 2.8 and 10.5 mg/l, respectively.

The oral absorption, distribution, metabolism and excretion studies described above are summarized in Table 9b at the end of this section.

Sodium Salicylate

There are animal and human data on the absorption, distribution, metabolism, and excretion of Sodium Salicylate given orally.

Animal Data

Groups of 10 rats were dosed orally on day 11 of gestation with Sodium Salicylate in 2% methylcellulose (equiv. to 500 mg/kg Salicylic Acid), and the amount of total salicylate in the plasma and in brain homogenate was determined (Davison et al., 1961). After 20 min, 296 and 38 mg/l free salicylate were found in the plasma and brain, respectively. After 60 min, these values were 316 and 52 mg/l, respectively.

Gravid Wistar rats were dosed orally with 500 mg/kg Sodium Salicylate; one group of animals was pretreated with 510 mg/kg benzoic acid 2 h before dosing (Kimmel et al., 1971). Urine was collected, and three animals per group were killed 3, 6, or 12 h after dosing, while one animal per group was killed 24 h after dosing. Maternal and fetal free salicylate was determined. Without benzoic acid pretreatment, the greatest concentration of free salicylate was seen 3 h after dosing, after which time the concentration declined. Without pretreatment, the 3 h salicylate concentration was approximately 450 µg/ml in maternal serum and 0.25 µg/mg in the fetus. Salicylate concentrations were similar in pretreated and nonpretreated animals at 3 h. However, with pretreatment, the salicylate concentration in both maternal serum and the fetus was greater at 6 and 12 h after dosing than it was at 3 h. The maximum salicylate concentration was seen at 6 h in maternal serum and 12 h in the fetus; these values were approximately 475 µg/ml and 0.26 µg/mg, respectively.

To study the pharmacokinetics and excretion of Sodium Salicylate, four New Zealand white rabbits were given a single oral dose of 44 mg/kg Sodium Salicylate, and blood samples and urine

were collected at various intervals for 36 and 96 h, respectively (Short et al., 1991). Plasma protein binding of Salicylic Acid was determined by adding radioactive Salicylic Acid to plasma to give final concentrations of 5, 50, and 500 µg/ml. Salicylic Acid was rapidly excreted in the urine, with slightly more than 50% of the dose eliminated as Salicylic Acid; 4% of the dose was excreted as SUA. Trace concentrations of sulfate conjugates were detected, and oxidative metabolites were not detected. Total recovery was 79.0%. SUA was only detectable in the plasma 30 h after dosing. The $t_{1/2}$ was 6.0 h. Plasma protein binding was concentration-dependent.

Human Data

A fasted male subject was given an oral dose of 579.7 mg Sodium Salicylate (equiv. to 500 mg Salicylic Acid), and urine was collected at various intervals (Farid et al., 1975). Within 96 h, a total of 12.7% of the dose was excreted as Salicylic Acid; 6.9 and 4.9% was excreted as Salicylic Acid 0-12 and 12-24 h after dosing, respectively.

The metabolism and excretion of Sodium Salicylate was determined using 44 male and 78 female black subjects (Emudianughe et al., 1986). The subjects were given an oral dose of 1 g Salicylic Acid as the sodium salt and urine was collected for 12 h. The mean total Salicylic Acid, free Salicylic Acid, salicyluric acid, Salicylic Acid glucuronide excreted by all subjects was 52.43, 6.62, 14.41, and 31.35%. For male subjects, these values were 60.59, 10.43, 6.53, and 43.63%, respectively, and for female subjects they were 47.8, 4.5, 18.94, and 24.35%, respectively. The salicyluric acid/Salicylic Acid glucuronide ratio was 0.64 for all subjects and 0.164 and 0.814 for male and females, respectively. Females excreted significantly more of the dose as salicyluric acid, while males excreted significantly more as Salicylic Acid glucuronide.

Influence of gender on the metabolism and excretion of Salicylic Acid was examined using seven male and seven female black Nigerian subjects (Emudianughe, 1988). The subjects were given an oral dose of 1 g Salicylic Acid as the sodium salt, and urine was collected hourly for 12 h. A mean of 48.72 and 53.63% of the total dose was excreted in 12 h by male and female subjects, respectively. Males excreted significantly less of the dose as free Salicylic Acid and SUA and significantly more as Salicylic Acid acyl glucuronide (SAAG) compared to females; males and females excreted 2.83 and 6.13% of the dose as free Salicylic Acid, respectively, 5.1 and 25.52% as SUA, and 40.48 and 21.96% as SAAG, respectively. The hourly M/F ratio for free Salicylic Acid were 1.3-4.1 and the hourly F/M ratios for SUA and SAAG were 2.1-10.8 and 0.30-1.30, respectively. The researchers stated that the results "suggest a possible genetic influence on the control of salicylic acid metabolism.

The pharmacokinetics of Salicylic Acid (as Sodium Salicylate) were determined using five male subjects (Shen et al., 1991). Each subject was given 3 g Salicylic Acid as Sodium Salicylate in 400 ml water prior to eating; food was allowed 2 h later. Blood and urine were collected at various intervals for 72 and 90 h, respectively. The mean total recovery was 98% of the dose; 13, 48, 20, 12, and 3.9% was Salicylic Acid, SUA, salicyl phenolic glucuronide, salicyl acyl glucuronide, and gentisuric acid, respectively. The lowest urinary pH values for individual subjects corresponded to the lowest unbound renal clearance.

To determine sex differences in absorption kinetics, six male and six female fasted subjects were given an oral dose of 9 mg/kg Sodium Salicylate in 200 ml water on five separate days; the days corresponded to days 2, 7, 14, 20, and 25 of the females' menstrual cycle (Miaskiewicz et al., 1982). Blood samples were obtained at various times 0 min-10 h after dosing. Five mos after the last dose, the subjects were given a 2 min intravenous (i.v.) infusion of Sodium Salicylate equivalent to the oral dose.

Mean kinetic values were similar for oral and i.v. administration. With the exception of plasma t_{max}, kinetic values were similar for males and females; t_{max} was less in males than females, i.e. 24-34 min for males and 37-60 min for females. The mean plasma C_{max} ranged from 65.8-71.0 for males and 55.2-63.7 for females. Throughout the month, no significant difference in salicylate distribution was seen. The mean oral and i.v. AUC, apparent $t_{½}$, apparent volume of distribution (aVd), and clearance were 331 and 333 mg/l·h, 4.4 and 5.0 h, 0.17 and 0.18 l/kg, and 27.5 and 27.4 ml/kg·h for males, respectively, and 304 and 334 mg/l·h, 4.1 and 4.6 h, 0.18 and 0.18 l/kg, and 29.9 and 27.0 m/kgl·h for females, respectively. When

the study was expanded to include 20 males and 20 females dosed orally, similar results were observed. Using 25 male and 25 female subjects in an equilibrium dialysis study, no sex differences in Sodium Salicylate plasma-binding were observed.

Abdallah et al. (1991) examined the effect of age on the pharmacokinetics of Sodium Salicylate. Twenty-two fasted male subjects, 30-85 years of age, were given an oral dose of 600 mg Sodium Salicylate (equiv. to 517.5 mg Salicylic Acid), and blood and urine samples were taken at various intervals for 24 and 48 h, respectively.

Creatinine clearance ranged from 58.8-168.8 ml/min and decreased significantly with age. Salicylic Acid was detected in the plasma within 10-30 min in all subjects; no measurable Salicylic Acid was detected in 14 subjects at 24 h. SUA concentrations rose and declined slowly; no measurable SUA was recovered at 24 h. Urinary recovery of the dose was 95% at 48 h; most of the dose (80%) was excreted as SUA, while only a mean of 5% of the dose was excreted as unchanged Salicylic Acid.

The C_{max} of Salicylic Acid ranged from 41.6-81.1 µg/ml; the aVd ranged from 7-14 l and increased significantly with age. Renal clearance was "low and highly variable" (1.4 ml/min), while oral clearance was 28.6 ml/min; neither appeared to correlate with age. The terminal rate constant of Salicylic Acid was 0.193/h and the terminal $t_{1/2}$ was 2.5-5.2 h. The SUA C_{max}, which ranged from 1.6-4.8 µg/ml, increased significantly with age. Renal clearance of SUA decreased significantly with age and had a positive correlation with creatinine clearance. The researchers concluded that the data suggested that age has a minor influence on the disposition of salicylate in male subjects.

Four male subjects were given 650 mg salicylate in the form of two tablets four times daily for 3 days (Porat-Soldin and Soldin, 1992). Blood and semen samples were obtained approximately 6 h after the last dose. The serum salicylate concentrations ranged from 21-170 mg/l and the semen salicylate concentrations ranged from 3-33 mg/l. Salicylate significantly reduced sperm motility.

A fasted male subject was given a single oral dose of 1 g Salicylic Acid (as the sodium salt) (Vree et al., 1994a; 1994b). In one experiment, the urine was kept acidic by administration of 1.2 g ammonium chloride four times a day and in a second experiment, the urine was kept alkaline by the administration of 3 g sodium bicarbonate four times a day.

When the urine was kept acidic, Salicylic Acid and its metabolites had a terminal $t_{1/2}$ of 3 h. Approximately 85% of the dose was excreted in the urine, predominantly as SUA (68.7%) and the glucuronides Salicylic Acid phenol glucuronide (SAPG) (4.9%), SAAG (6.0%), and SUA phenolic glucuronide (SUPG) (5.2%). Only 0.6% of the dose was excreted as unconjugated Salicylic Acid. Salicylic Acid had a renal clearance of 0.16 ml/min. When the urine was kept basic, the terminal $t_{1/2}$ was 2.6 h. Approximately 91% of the dose was excreted in the urine, again predominantly as SUA (58.3%). The amount of the dose excreted as unconjugated Salicylic Acid was 22.2%. The amount excreted as glucuronides was 4.7% as SAPG, 2.3% as SAAG, and 3.9% as SUPG. Salicylic Acid had a renal clearance of 9.0 ml/min.

The dermal absorption, distribution, metabolism, and excretion studies described above are summarized in Table 8b.

ORAL MUCOSAL ROUTE OF ADMINISTRATION

Salicylic Acid

There are animal data only on the absorption, distribution, metabolism, and excretion of Salicylic Acid through the mucous membranes of the oral cavity.

Animal Data

Tanaka et al (1980) extended their work to evaluate the role of absorption of Salicylic Acid through the mucous membrane of the oral cavity. The absorption of Salicylic Acid from a number of different vehicles into the oral mucous membrane of the cheek was determined using male golden hamsters (Tanaka et al., 1980). One g of each ointment containing 2% Salicylic Acid was placed on the inside cheek of the animals using a syringe; swallowing was prevented. Blood was collected for up to 5 h. The amount of Salicylic Acid in the tissue of the cheek pouch and the

residual Salicylic Acid was determined.

The Salicylic Acid blood concentration peaked after 30 min at approximately 70 µg/ml with the hydrophilic base (25% white petrolatum, 22% stearyl alcohol, 12% propylene glycol, and 1.5% SLS) and after 1 h at approximately 100 µg/ml with the "absorption ointment" (40% white petrolatum, 18% cetyl alcohol, and 5% sorbitan oleate). It did not peak until 3 h with the PEG ointment (49% each PEG-8 and PEG-90) and the white petrolatum ointment, and the peaks were at approximately 35 and 20 µg/ml, respectively. The k_as for the hydrophilic, absorption, PEG, and petrolatum ointments were 5.13, 2.92, 0.36, and 0.56/h, respectively, and the k_{el}s were 0.36, 0.37, 0.30, and 0.33/h, respectively. The AUCs were 182, 235, 145, and 70 for the hydrophilic, absorption, PEG, and petrolatum ointments, and the total absorption concentration/distribution volumes were 81, 102, 74, and 34, respectively.

A base containing 35% petrolatum, 10% cetyl alcohol, and 5% of hexadecyl alcohol, lanolin, and sorbitan oleate had the greatest AUC and total absorption concentration/distribution volume, 459 and 216, respectively. In the cheek pouch, the change in Salicylic Acid concentration was greatest in the absorption and hydrophilic bases; the loss of Salicylic Acid from the bases was greater than the total quantity of Salicylic Acid recovered in the blood. A "relatively high concentration" of Salicylic Acid was detected in the tissue of the cheek pouch.

Kurosaki et al. (1988) examined the effect of surfactants on the absorption of Salicylic Acid from the keratinized mucosa of the cheek pouch of male golden hamsters. Absorption was measured at pH 3.0, 4.0, and 7.0 alone and with SLS, cetylpyridinium chloride, polysorbate-80, and sodium taurocholate. At 1 h, absorption of Salicylic Acid alone was 49.8% at pH 3.0 and 0.2% at pH 7.0. At pH 7.0, 20 mM SLS significantly increased absorption of Salicylic Acid to 8%; no effect was seen at the lower pHs. Cetylpyridinium chloride and polysorbate-80 decreased absorption of Salicylic Acid at the lower pHs. Sodium taurocholate did not affect absorption. The degree of Salicylic Acid-surfactant interaction was determined; only polysorbate-80 and cetylpyridinium chloride interacted with Salicylic Acid and the interaction was strongest with the latter.

The effect of pretreating the cheek pouch with the surfactants was examined. Absorption of Salicylic Acid was significantly increased with pretreatment with 20 mM SLS and cetylpyridinium chloride. At pH 7.0, absorption at 1 h was 1.4% without pretreatment, 1.9, 8.5, and 19.0% after pretreatment with 1.0, 5.0, and 20.0 mM SLS, respectively, and 2.8, 6.2, and 10.3% after pretreatment with 1.0, 5.0, and 20.0 mM cetylpyridinium chloride, respectively. The difference in absorption after pretreatment with the surfactants was significant at 20 mM.

The oral mucosal absorption, distribution, metabolism and excretion studies described above are summarized in Table 8c.

PARENTERAL ROUTE OF ADMINISTRATION

Salicylic Acid

There are animal and human data on the absorption, distribution, metabolism, and excretion of Salicylic Acid given parenterally.

Animal Data

Dogs were dosed i.v. with 1 g ^{14}C-Salicylic Acid (containing 10 µCi) in sodium bicarbonate solution (Alpen et al., 1951). Urine was collected for 30-36 h. Urinary metabolite recovery from one animal, which was representative of all the dosed animals, was 50% unchanged Salicylic Acid, 25% glycuronates, 10% salicyluric acid, and 4-5% gentisic acid. Total recovery was >90% of the dose.

Koshakji and Schulert (1973) demonstrated that Salicylic Acid can readily penetrate into fetal circulation. Four gravid Sprague-Dawley rats were given a s.c injection of 300 mg/kg Sodium Salicylate (177.4 mg/ml) containing 10 µCi/ml carboxyl-^{14}C-Salicylic Acid, and the animals were killed 1 h later. The percent of injected ^{14}C dose/g dry wt of fetal tissue was 4.06.

The transport of Salicylic Acid across the blood-testis barrier of male Charles River rats was determined by continuous i.v. infusion and measurement of Salicylic Acid concentration in rete testis fluid (Okumura et al., 1975). The transfer rate of Salicylic Acid from plasma to rete testis fluid was stated to be 0.0041/min. Permeability across the blood-testis barrier

correlated with partition coefficient; Salicylic Acid has a pK_a of 3.0.

Four pregnant, near-term >137 days gestation) Suffolk or Suffolk-Dorset ewes were dosed i.v. at time 0 and 180 min with a bolus of ^{14}C-Salicylic Acid (56-187 µCi) and ^{3}H-acetylsalicylic acid (99-173 µCi) (Thiessen et al., 1984). An infusion of 42 µg/kg/min non-radioactive acetylsalicylic acid was started at 60 min. Blood samples were taken at various intervals from 0-240 min. Thin layer chromatography was used to determine plasma drug concentrations. Both Salicylic Acid and acetylsalicylic acid crossed the placental barrier, and equilibrium was reached approximately 40 min after salicylate administration. The average equilibrium plasma fetal/maternal ratio was 0.4. The mean clearance in the ewe was 358 ml/min for Salicylic Acid and 764 ml/min for acetylsalicylic acid.

Groups of 3 and 25 mos old male Fischer 344 rats were dosed i.v. with 5 or 50 mg/kg ^{14}C-Salicylic Acid (25 µCi/kg) in an Emulphor:ethanol: water (1:1:4) solution at a volume of 1 ml/kg (McMahon et al., 1990). In both groups, plasma salicylate concentrations ranged from 17-28 µg/ml and 100-120 µg/ml with doses of 5 and 50 mg/kg, respectively. The $t_{1/2}$s in 3 mos old animals were 4.08 and 30.1 h with doses of 5 and 50 mg/kg, respectively; these values were 21.3 and 21.9 h, respectively, in 25 mos old animals. No Salicylic Acid metabolites were detected in the plasma.

A perfused rat liver study was performed to determine whether the liver was a major site of metabolism of Salicylic Acid (Shetty et al., 1994). Hepatic metabolism of Salicylic Acid was negligible during a single pass through the liver. The addition of glycine, glucose, or bovine serum albumin to the perfusate did not affect hepatic uptake or metabolism.

Human Data

Human subjects (number not stated) were dosed i.v. with ^{14}C-Salicylic Acid (Feldmann and Maibach, 1970). After 4 h, 89.8% of the radioactivity was recovered in the urine.

Sodium Salicylate

There are animal and human data on the absorption, distribution, metabolism, and excretion of Sodium Salicyate given parenterally.

Animal Data

A gravid rabbit was given a single s.c. dose of 1 g/kg and another rabbit was given a dose of 1.5 g/kg Sodium Salicylate, both on day 30 of gestation, and blood was taken and the uterus removed from both animals 2 h after dosing (Jackson, 1948). In the animal dosed with 1 g/kg, the maternal serum salicylate concentration was 0.58 mg/ml and the pooled fetal serum concentration was 0.37 mg/ml. In the animal dosed with 1.5 g/kg, the maternal serum salicylate concentration was 0.75 mg/ml and fetal serum concentrations ranged from 0.45-0.62 mg/ml.

The distribution of Sodium Salicylate was investigated in non-gravid A/Jax mice and gravid A/Jax and CBA mice (Eriksson and Larsson, 1971). Groups of three to five animals were dosed i.m. with radioactive Sodium Salicylate at a volume of 0.1 ml/20 g body wt, which corresponded to 1 µCi Salicylic-1-^{14}C-Acid in 10 mg Sodium Salicylate. Gravid animals were dosed either on day 14 of gestation and killed 30 or 240 min after dosing or on day 17 of gestation and killed 30, 60, 120, 240, or 480 min after dosing. Non-gravid animals were killed 30, 120, or 240 min after dosing.

The amount of radioactivity in the blood was greater in non-gravid than gravid animals. On day 14 of gestation, the blood radioactivity concentrations varied within the same strain of mouse at each time period; additionally, the concentrations were generally greater in the CBA than A/Jax mice. In animals dosed on day 17 of gestation, blood radioactivity was variable but a strain difference was not seen. The decrease in radioactivity in the blood of these animals was greatest 4-8 h after dosing. In non-gravid mice, blood radioactivity concentrations decline linearly between 20 and 240 min to approximately 60% of the earlier value. In both gravid and non-gravid mice, the hepatic radioactivity concentrations were relatively unchanged with time. For animals dosed on days 14 and 17 of gestation, the fetal radioactivity concentrations were initially greater in CBA mice but then decreased to those of A/Jax mice. For mice dosed on day 14 of gestation, average A/Jax fetal radioactivity per litter was 31-41 and 33-46 cpm/mg at 30 and 240 min, respectively, and average CBA fetal radioactivity

per litter was 48-59 and 35-48 cpm/mg after 30 and 240 min, respectively. For mice dosed on day 17 of gestation, average radioactivity per litter in normal A/Jax fetuses was 32-37, 35-44, 32-44, and 36-45 cpm/mg after 30, 60, 120, and 240 min, respectively, and in normal CBA fetuses was 40-64, 43-50, 38-50, 32-44, and 16-19 cpm/mg after 30, 60, 120, 240, and 480 min, respectively.

Hemorrhages were observed in three A/Jax and three CBA fetuses after 240 min and in three A/Jax and at least seven CBA fetuses after 480 min. Radioactivity was 37-53 and 25-28 cpm/mg in A/Jax fetuses 240 and 480 min after dosing, respectively, and 35-55 and 16-26 cpm/mg in CBA fetuses 240 and 480 min after dosing, respectively. At least 13 A/Jax fetuses and six CBA fetuses from dams killed 480 min after dosing were dead. The radioactivity in these fetuses was 20-26 and 21-32 cpm/mg, respectively.

Eriksson and Larsson (1971) also pretreated gravid A/Jax mice with non-radioactive Sodium Salicylate at a dose of 3 mg/20 g body wt on days 15 and 16 of gestation, and then dosed them with the radioactive solution on day 17 of gestation. The animals were killed 30, 60, 120, or 240 min after the last dose. Pretreatment with Sodium Salicylate increased the variability of the radioactivity in the blood between animals of the same groups. Maternal blood, maternal hepatic, and neonatal radioactivity concentrations were similar to those seen in the animals that were not pretreated.

Rabbits were dosed i.v. with 5 ml of a 4 g ^{14}C-Sodium Salicylate (200 µCi) in 110 ml distilled water solution, and blood samples were taken at various times from 15-360 min after dosing (Schuppli et al., 1972). The approximate $t_{1/2}$ was 1.5-4 h.

Six rats or six ferrets per group were used to determine the concentration of Sodium Salicylate in blood following a single s.c. dose of 125 or 400 mg/kg (Gulamhusein et al., 1980). Blood samples were taken 1, 2, 3, and 24 h after dosing. After 1 h, the blood salicylate concentration was 54 and 54.4 mg% in rats and ferrets, respectively, dosed with 400 mg/kg and 30 and 28 mg%, in rats and ferrets, respectively, dosed with 125 mg/kg. These values gradually decreased at 2 and 3 h, and were similar to blank samples at 24 h.

The pharmacokinetics of Sodium Salicylate were determined in male and female Sprague-Dawley rats of various ages (Varma and Yue, 1984). The animals were given i.v. injections of 62 µmol/kg Sodium Salicylate. Older animals tended to have higher plasma concentrations of Salicylic Acid. The pharmacokinetics are summarized in Table 7.

Table 7. Pharmacokinetics of Sodium Salicylate in Male and Female Rats of Different Ages Given i.v. Injections (Varma and Yue, 1984)

	$t_{½}$ (h)		aV_d (ml/kg)		Plasma clearance (ml/kg/h)		Plasma Salicylic Acid concentration at 6 h (nmol/ml)	
Age (wks) / Sex	Male	Female	Male	Female	Male	Female	Male	Female
1	13.9	12.0	433*	391*	22.0	25.0	125-150	100-150
3	2.5*	2.7*	149	201	44.0*	54.0*	50-113	50-81
8-9	6.6	7.3*	213**	144	23.2**	13.8	144-209	250-306
14-15	7.1**	11.9	186**	150	18.6**	8.9	125-250	159-388
56-60	10.4	15.7	165	175	13.5**	7.9	188-269	206-356

*value significantly different from all other values in same column
**value significantly different from corresponding female animals

Following dosing, Salicylic Acid was the only compound found in the serum of the test animals. Urinary excretion of Salicylic Acid and SUA was similar for male and female animals. In pregnant rats, the volume of distribution was greater than in adult female rats, while the other parameters were similar.

Salicylate distribution was compared in gravid and non-gravid female (control) Wistar ST rats following i.v. administration (Yoshikawa et al., 1984). The gravid animals were given a single dose of 10 mg/kg Sodium Salicylate containing 5 µCi/kg ^{14}C-Sodium Salicylate on day 20 of gestation, and the controls were given the same dose. Blood sample were obtained at 0.5 and 1-8 h after dosing, and the animals were killed after 8 h. Approximately 10 fetuses were obtained from gravid animals. Serum protein binding was determined using serum obtained after 8 h.

Serum salicylate concentrations were significantly decreased in gravid animals compared to controls, although serum $t_{1/2}$s were similar; this was attributed to an approximately 40% increase in the distribution volume of gravid animals. An increase in total body serum clearance was also observed for gravid animals. The fetal serum salicylate concentration was not significantly different from the maternal concentration. The average serum salicylate concentrations in control, gravid, and fetal animals were 34.3, 21.7, and 22.5 µg/ml, respectively; the unbound fractions were 0.137, 0.667, and 0.018, respectively.

The serum unbound salicylate fraction in both control and fetal animals increased with increasing concentrations of Sodium Salicylate, while the value in the gravid animals was constant. In gravid animals, the serum protein binding of salicylate was greatly decreased, but the binding of salicylate to serum was linear over a wide concentration range. The researchers also determined the tissue-to-serum partition coefficients (K_p) for a number of tissues; the K_p values were significantly greater in all tissues except the liver in gravid rats compared to controls. The fetal K_p values were significantly increased in all tissues except the lungs and kidneys compared to maternal values.

Yoshikawa et al. (1984) also determined the blood-to-plasma concentration ratio of Sodium Salicylate using blood pooled from five gravid and five non-gravid female Wistar rats. The pooled blood was incubated with 100 nCi/ml ^{14}C-Sodium Salicylate and 20-160 µg/ml non-radioactive Sodium Salicylate for 20 min. The ratios were "almost constant" in this concentration range, and the average calculated ratios were 0.74 and 0.60 in the gravid and control animals, respectively.

Groups of three to nine gravid Sprague-Dawley rats were given a single i.v. injection of 15, 50, 100, 200, or 500 mg/kg Sodium Salicylate on day 8 of gestation (Gabrielsson et al., 1985). Blood samples were taken at various intervals at 1 min to 30 h after dosing. After 1 min, a dose of 500 mg/kg Sodium Salicylate resulted in a peak plasma concentration of 1800 µg/ml with a "typical non-linear" pharmacokinetic behavior. Doses of 100 and 200 mg/kg Sodium Salicylate resulted in the same but less pronounced pattern, with peak plasma concentrations at 1 min of 600 and 900 µg/ml, respectively. After 1 min, doses of 15 and 50 mg/kg resulted in peak plasma concentrations of 100 and 300 µg/ml, respectively, with a linear pharmacokinetic behavior.

Gabrielsson et al. (1985) also gave 14 or 12 gravid animals constant infusions of 1 or 2 mg/h Sodium Salicylate, respectively, on days 6-13 of gestation, and blood samples were taken on the days of dosing. In the animals given 1 mg/h, the plasma concentration peaked on days 6 and 8 of dosing at approximately 110 µg/ml, and were in the range of 50-110 µg/ml during dosing. In the animals given 2 mg/h, plasma concentrations peaked on day 8 of gestation at approximately 240 µg/ml, and were in the range of 150-240 µg/ml during dosing.

Groups of five gravid hooded Wistar rats were given a single i.v. dose of Sodium Salicylate (equiv. to 50 mg/kg Salicylic Acid) on day 20 of gestation, and a control group of five non-gravid animals were dosed in the same manner (Dean et al., 1989). Blood samples were taken at various intervals and urine was collected for 24 h following dosing. Absolute total body clearance of salicylate was similar between the groups, but the absolute aVd was significantly increased in gravid animals as compared to controls. Normalized values (adjusting for increased body weight) indicated a significant reduction in total body clearance, with only a slight increase in the aVd. The $t_{½}$ of salicylate was significantly

increased in the gravid animals. Urinalysis indicated that gravid animals excreted less of the administered dose than controls. Also, the metabolic profile was changed in gravid animals. Salicylate serum protein binding was decreased in gravid animals compared to controls; in both groups, binding decreased "in an essentially parallel fashion" with increased salicylate.

Gravid Sprague-Dawley rats were given a constant-rate i.v. infusion of 150 mg/kg/day Sodium Salicylate (at an infusion rate of 10 µl/h) on days 6-13 of gestation (Bergman et al., 1990). Blood salicylate concentrations were 112-141 µg/ml, with a mean of 120 µg/ml, on days 7-13 of gestation.

To study the pharmacokinetics and excretion of Sodium Salicylate, four New Zealand white rabbits were given a single i.v. dose of 44 mg/kg Sodium Salicylate, and blood samples and urine were collected at various intervals for 36 and 96 h, respectively (Short et al., 1991). Plasma protein binding of Salicylic Acid was determined by adding radioactive Salicylic Acid to plasma to give final concentrations of 5, 50, and 500 µg/ml. Salicylic Acid was rapidly excreted in the urine, with slightly more than 50% of the dose eliminated as Salicylic Acid; 4% of the dose was excreted as SUA. The sulfate conjugates of Salicylic Acid and SUA accounted for 7.25 and 2.3% of the excreted dose, respectively; the oxidative metabolites were not detected. Total recovery was 85.8%. SUA was only detectable for 120 h after dosing. The $t_{1/2}$ was 4.3 h. Plasma protein binding was concentration-dependent.

Human Data

Human subjects (number not specified) were dosed i.v. with 250 mg Sodium Salicylate (equiv. 215.7 mg Salicylic Acid), and the absorption rate was determined using urinary excretion (Wurster and Kramer, 1961). Urine was collected every 2 h for 24 h. The total amount of salicylate recovered in the urine varied from 83.8-94.5% of the dose.

The parenteral absorption, distribution, metabolism and excretion studies described above are summarized in Table 8d.

Table 8a. Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
			SALICYLIC ACID (SA)	
Landrace pig skin	0.25-2.0 mg/ml, pH 2.2-7.5	ear skin	The rate of penetration was proportional to the conc. at pH 2.2, ranging from 0.1-1.4 mg/cm^2/24 h with 0.25-2 mg/ml W/1 mg/ml, the approximate penetration rates were 1.5, 0.75, 0.5, 0.4, 0.375, and 0.375 mg/cm^2/24 h at pH 2.6, 3.5, 4.2, 4.4, 5.5, and 7.75	Loveday, 1961
hairless mouse skin	undiluted in 6 vehicles	not stated	The permeability coefficients were 21.2, 21.0, 11.2, 4.8, 2.1, and 7.9 cm/h w/oleic acid, isopropyl myristate, 1-octantol, 1-propanol, propylene glycol, and formamide, respectively	Sloan et al., 1983
female fuzzy rats	5 µg/cm^2 in acetone	back skin	Most radioactivity was found in the receptor fluid; 12.2 and 7.7% of the dose was found in the fluid and skin, respectively None of the absorbed SA was metabolized	Bronaugh et al., 1989; 1989-90
intact hairless mouse skin	1%, pH 4.0	diffusion cell	A zero-order penetration pattern was observed; approx. 14 µmol penetrated after 10 h	Higo et al., 1995
10 NZW rabbits/gp	6% in an oleaginous, hydrophilic, o/w, or water-soluble base	7.5 g was applied to the back under an occlusive patch for 9 h	Absorption was greatest from the o/w ointment, w/peak absorption of 11.0 mg% at 5 h Peak absorption from the hydrophilic and oleaginous base was 8.8 and 6.8 mg% at 6 and 4 h; absorption from the water-soluble base was negligible	Stolar et al., 1960

Table 8a (con't). Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA) - continued		
4 NZW rabbits/gp	10% in hydrophilic ointment, hydrophilic petrolatum, PEG ointment, or steareth-20 gel	Ointments were applied under an occlusive patch to shaved dorsal skin for 8 h w/out and w/DMSO	Blood salicylate conc. peaked at: Hydrophilic ointment: 5 and 2 h w/out and w/DMSO Hydrophilic petrolatum: 8 and 3 h w/out and w/DMSO PEG ointment: 8 and 6 h w/out and w/DMSO Steareth-20 gel: 3 and 4 h w/out and w/DMSO	Stelzer et al., 1968
guinea pigs	200, 400, and 1000 µg/ml at pH 3; 500 µg/ml at pH 2, 3, 4, 5, 7, 8, 9, 10	Applied to abdominal skin using a recirculation device	At pH 3.0, rate of absorption was independant of concentration (approx. 4%); at 500 µg/ml, absorption decreased from 6.1% at pH 2 to zero at pH 5 and 7 then up to 15.5% at pH 10.	Arita et al., 1970
4 NZW rabbits/gp	10% in hydrophilic ointment at pH 2.97, 4.48, 6.8, 9.23, and 10.78	Ointments were applied under an occlusive patch to shaved dorsal skin for 7.5 h w/out and w/DMSO; blood samples were taken at 1.5 h intervals	W/out DMSO, the SA blood conc. incr. at each time interval w/pH 2.97-6.8, peaked at 6.0 h w/pH 9.23, and at 4.5 h w/ pH 10.78 W/DMSO, the SA blood conc. peaked at 6.0 h w/pH 2.97 and 4.48, at 4.5 h w/pH 6.8 and 9.23, and at 3.0 h w/pH 10.78 The blood salicylate conc. were greater w/DMSO	Marcus et al., 1970
male SD rats	soln w/5% ethanol, pH 2, 3, 6, or 8	The tails were immersed in solution	The total amount absorbed at pH 2 and 3 was 0.64 and 0.33 µg/mm^2/h; no SA was absorbed at pH 6 or 8	Siddiqi and Ritschel, 1972
guinea pigs	3% in water, 50% ethanol, or 75% ethanol	Application to the back of each animal for 1 h; the animals were then killed and the skin removed and tape-stripped	Absorption was greatest from the 75% ethanol vehicle (106.1%) of the applied dose and least from water (56.9% of the dose) Most of the radioactivity was found in tape strips 1-5	Yankell, 1972
3 guinea pigs	3% in 75% ethanol	Application to the lower back for 24 h; the animals were then killed	Most of the radioactivity was recovered in the feces (401.2-808.5% applied dose x 10^3) and the treated back muscle (161.1-686.3% applied dose x 10^3)	Yankell, 1972
damaged guinea pig skin	250-1000 µg/ml, pH 2-6	Applied to abdominal skin *in vitro* using a recirculation device	500 µg/ml, pH 3 - absorption rate of 79.4% Rate of absorption was independent of concentration, but increased w/an incr. fraction of un-ionized form	Washitake et al., 1973
	500 µg/ml, pH 3	Animals were exposed for 0.5-6 h and then killed; the skin was isolated to the corium	The amount of SA reserved in the skin peaked at 0.5-1 h, independant of concentration (250-1000 µg/ml); Varying the pH from 3-6 resulting in a lower and broader peak that took longer to reach	
	500 µg/ml, pH 3	Animals were exposed to recirculation for 1 h and then killed after 0.5-24 h	The amount of SA found in the skin decreased rapidly w/time	
8 rabbits	36.2 mmol/100 g	Patches of 5 g of salve applied for 6 h	5.5 and 11.08% of the dose was excreted after 24 and 48 h, respectively	Panse et al., 1974
guinea pig	500 µg/ml in hexadecyl alcohol, oleic acid, or isopropyl myristate; 75-300 µg/ml in liquid paraffin	A recirculation device was attached to the shaved abdomen; skin was intact or tape stripped Animals were killed at various intervals for up to 6 h	Intact skin: 14.6, 1.7, 1.6, and 1.5% of the SA was absorbed from liquid paraffin, isopropyl myristate, hexadecyl alcohol, and oleic acid Less SA was retained in damaged skin than intact skin; w/damaged skin, the amount of SA retained in solution decr. w/time No saturation phenomenon was observed w/absorption from liquid paraffin	Washitake et al., 1975
		Adsorption was determined *in vitro*	3.56, 2.26, 1.57, and 0.73 mg was adsorbed from liquid paraffin, isopropyl myristate, hexadecyl alcohol, and oleic acid, respectively	

Table 8a (con't). Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA) - continued		
NZW rabbits	10% in petrolatum alone, w/10% DMSO, or 10% DMSO and 10% surfactant	The ointments were applied under an occlusive patch to shaved dorsal skin for 8 h; blood samples were taken hourly	The greatest peak blood salicylate conc. were seen w/SA, DMSO, and either oleth-2, sorbitan laurate, or sorbitan trioleate, 12.5 mg% at 2, 3, and 2 h, respectively SA in petrolatum w/out DMSO and surfactant only had a peak value of 3 mg% at 7 h	Shen et al., 1976
≥3 female Wistar rats/gp	1, 5, or 10% in a hydrophilic ointment	The ointments were applied to a shaved flank under an occlusive patch daily for 5 days or weekly for 4 wks Treated skin was excised, the appropriate ointment applied, and the sample placed in a diffusion cell	A single application of 1, 5,and 10% had a mean penetration flux of 0.014, 0.061, and 0.078 mg/cm^2/h W/repeated daily doses, a sig. difference in flux was seen between doses; the flux incr. w/1% until day 4, while w/ 5 and 10% it decr. after day 3 The weekly penetration flux of 1% remained constant, while that of 5 and 10% decr.; difference between 5 and 10% was sig.	Roberts and Horlock, 1978
4 female Rhesus monkeys	4 mg/cm^2	Applied to the abdomen as both a single dose and daily for 14 days	Single dose: 59% SA cumulative absorption Multiple dose: 67 and 78% cumulative absorption after 1st and 8th dose	Bucks et al., 1990
male Wistar rats	1 mM in 20mM HEPES buffer (pH 7.4)	Using glass diffusion cells, absorption was measured w/out and w/iontophoresis in the epidermis and the dermis	The absorption rate constant, clearance, and percent dose applied was 0.0028/min, 0.50 ml/h, and 22.7% w/epidermal iontophoresis and 0.0032/min, o.58 ml/h, and 34.3% w/passive dermal absorption	Singh and Roberts, 1993
Wistar rat skin	1 mM in 20mM HEPES buffer (pH 7.4)	Measured through the dermis *in vitro* using diffusion cells	The permeability coefficient was 0.013 cm/h	Singh and Roberts, 1993
male Wistar rats	not given	Applied to the exposed epidermis of the dorsum of anesthetized rats in a glass cell and epidermis removed postmortem	Dermal clearances were 0.58 and 0.10 ml/h for epidermis in anesthetized and postmortem	Singh and Roberts, 1994
human skin	5% in 5 vehicles	Leg and/or breast skin *in vitro* in a corium spot test	Penetration was greatest with lanolin, Plastibase®, and Hydrophilic Plastibase®, moderate from carbowax, and minimal from petrolatum	Flesch et al., 1955
human skin - male	5%	Abdominal and leg skin samples	Dermal penetration steadily incr. between 10-20 h Mean penetration through abdominal (8 samples) and leg (6 samples) stratum corneum and was 3.6 and 5.7 µM/cm^2/ 24 h	Elias et al., 1981
human skin	10 mg in a Aqueous emulsion	Applied to a 4 cm^2 area of excised skin; 20 tape-strippings were removed	20.5 and 20.7% of the dose penetrated the horny laver after 30 and 60 min; 12.7 and 10.9% remained in the emulsion After 30 min, the greatest SA content was in tape strippings 1-5 (7-16 µg) and 5-10 (5-8 µg); the same trend was observed after 100 min	Neubert et al., 1990
human skin	10 mg in a Aqueous emulsion or vaseline	Applied to a 4 cm^2 area using a 3-membrane system	Vaseline: 9, 6, and 5% (30 min) and 10, 9, and 9.2% (60 min) of the dose penetrated membranes 1, 2, and 3 Aqueous emulsion: 21.3, 12.9, and 8.4% (30 min) and 17.8, 15.8, and 14.9% (60 min) of the dose penetrated layers 1, 2, and 3	Neubert et al., 1990

Table 8a (con't). Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA) - continued		
human and rodent skin	500 µg/ml *in vitro* (pH 2-4)	Applied to a 0.785 cm^2 area of skin in a Franz cell	At pH 4, SA penetrated in a zero-order fashion following a lag time When comparing penetration at pH 2-4, it was always greatest at pH 2 (in both various human samples and rodent samples) Age did not affect penetration through human breast skin	Harada et al., 1993
human dermis	1 mM in 20mM HEPES buffer (pH 7.4)	Applied to excised midabdominal dermis in a diffusion cell	The dermal permeability coefficient was 0.017 cm/h	Singh and Roberts, 1993
human epidermis	Concentration not given; pH 7.4 (100% ionization) and at pH of 50% ionization	Applied to excised midabdominal epidermis at full and 50% ionization	The permeability coefficients were 0.000331 and 0.0152 cm/h at 100 and 50% ionization	Singh and Roberts, 1994
17 humans	4 µg/cm^2	Open application to the ventral forearm	Total absorption was 22.78% over 5 days; the greatest absorption rate, 0.535%/h, was observed at 12-24 h	Feldmann and Maibach, 1970
21 humans w/dermatoses	therapeutic levels	Applications were made to large areas of the body	Average plasma SA concentration was 5.4 mg%	Schuppli et al., 1972
10 male humans	9.10 mg/kg	0.5 g of salve applied to the trunk and extremities	Mean urinary excretion was 0.417, 0.572, and 1.060% after 12, 24, and 48 h, respectively	Panse et al., 1974
4 humans w/active psoriasis	6% in 60% propylene glycol/ 19.4% alcohol gel	Occluded application to the entire body below the neck for 10 h; repeated for 5 days	Absorption ranged from 63-82%; dose was excreted in the urine as 41-65% SUA, 32-57% acyl and phenolic glucuronides of SA, and 0-14% SA	Taylor and Halprin, 1975
2 humans /gp	3% in 40% PEG-8	Forearm was immersed for 3 h	Minimal systemic absorption; keratolysis was observed w/in 24 h	Birmingham et al., 1979
2-4 humans	10% in hydrophilic ointment	Forearm - site was occluded for 3 h; in 2 subjects, the area was tape-stripped prior to application	Intact skin - SA was not detected in the blood Taped-stripped skin - appreciable SA absorption; peak concentration (conc.) - 8 mg/dl; k_a - 0.189/h; k_{el} - 0.201/h; $t_{1/2}$ - 3.45 h	
15 humans	0.33 g/l	20 min bath	Mean plasma SA concentrations ranged from 9.5-10.80 ng/ml over 24 h; 0.086 and 0.078 mg SA excreted, repspectively and 0.92 and 0.72 mg SUA excreted, respectively in the urine at 0-24 and 24-48 h	Pratzel et al., 1990
6 humans	3% w/0.1% DFV	20 g twice daily for 22 h for 8 days to the trunk, upper arms, and thighs	Plasma SA conc. increased (incr.) during the day from 2-3 to 4-7 µg/ml; AUC was 30 µg·day/ml	Täuber et al., 1993
9-10 human females w/normal skin 9 w/acnegic skin	2% in hydroalcoholic vehicle; 2% in cream	1.25-1.5 g to the face and neck for 16 days	Steady-state was reached by day 7 Peak plasma conc. was reached earlier and AUC was greater w/the hydroalcoholic vehicle Terminal $t_{1/2}$ was not affected by skin type or vehicle	Davis et al., 1997
6 humans	39.7 µg/cm^2 in ethanol	Open application to the ventral forearm for 24 h	Mean 7-day urinary excretion of Salicylic Acid (SA) was 5.8%; 53.4% was recovered in the wash and 0.22% was recovered in tape strippings	Wester et al., 1998

Table 8a (con't). Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA) - continued		
9 male and 7 female humans	5% w/v SA solution	Microdialysis was used; 5 ml was added to the chambers using normal and damage skin	Absorption was significantly increased in damaged skin compared to normal skin	Benfeldt et al., 1999
		SODIUM SALICYLATE (SS)		
10 NZW rabbits/gp	6.95% in an oleaginous, hydrophilic, o/w, and water-soluble base	7.5 g was applied to the back under an occlusive patch for 9 h	Absorption was greatest from the o/w ointment, w/peak absorption of 4.6 mg% at 5 h Absorption from the oleaginous and hydrophilic bases were 1.0 and 0.4 mg% at 6 and 5 h; absorption was negligible from the water-soluble base	Stolar et al., 1960
4 NZW rabbits/gp	11.6% from hydrophilic and hydrophilic petrolatum bases	Application under an occlusive patch to shaved dorsal skin for 8 h w/out and w/DMSO	Blood salicylate conc. peaked at 8 h w/all ointments; values were: 4.03 mg% from the both bases w/out DMSO and 1.38 mg% from both bases w/DMSO	Stelzer et al., 1968
NZW rabbits	alone, w/DMSO, or w/DMSO and surfactants	Application under an occlusive patch to shaved dorsal skin for 8 h; blood samples were taken hourly	The greatest peak blood salicylate conc. was seen w/SS, DMSO, and poloxamer 182, 3.5 mg% at 4 h, followed by SS, DMSO, and either poloxamer 231 or oleth-2, 2.75 mg% at 3 or 5 h, respectively The least penetration was seen w/SS and DMSO, 1 mg% at 8 h	Shen et al., 1976
Guinea pigs	in water; equiv to 3% SA	Determined whether lateral diffusion occurred	Lateral diffusion did not occur; <2% of the applied dose was found in sites adjacent to the test site	Yankell, 1972
human skin	5% in 5 vehicles	Leg and/or breast skin	No penetration was observed w/petrolatum, carbowax, lanolin, Plastibase®, or Hydrophilic Plastibase® vehicle after 24 h	Flesch et al., 1955
human skin	in a Aqueous emulsion	The horny layer of excised skin and a 3-layer membrane system	19.0 and 23.2% of the Sodium Salicylate (SS) penetrated the horny layer after 30 and 60 min; 26.6 and 24.1% remained in the emulsion After 30 min, the greatest SS was in tape stripping 1-5 (5-27 µg) With the membrane system, 20.3, 6.6, and 3.1% and 26.0, 9.5, and 5.5% of the dose penetrated into layers 1, 2, and 3 after 30 min and 60 min	Neubert et al., 1990
		TEA-SALICYLATE		
8 rabbits	36.2 mmol/100 g	Patches of 5 g salve applied for 6 h	4.01 and 14.59% of the dose excreted in the urine after 24 and 48 h	Panse et al., 1974
5 male Beagle dogs	10 g	Massaged into the shaved right knee	After 60 min, salicylate conc. in the application site, synovium, synovial fluid, blood, and urine were 321.2,0.74, 0.80, 0.22, and 0.16 µg/ml	Rabinowitz et al., 1982
6 female Yorkshire swine	10%	Application of 1.5 g to a shaved 100 cm^2 area of the biceps femoris	After 2 h, ≥82% of the dose was absorbed, 7.9% remained on the skin, and 9.3% remained in skin tissue 150.9-724.5 ng/g and 313.5-582.3 ng/g were recovered in the treated muscle after 30 min and 2 h	Baldwin et al., 1984
5 male and 10 female Beagle dogs	10%	10 g massaged to a 100 cm^2 area of a shaved knee	After 60 min, salicylate conc. in the application site, synovial fluid, and serum were 50.9, 0.54, and 0.004 µmol/g	Rabinowitz and Baker, 1984
13 Beagle dogs	0.1, 1. or 5 g to make 10 g cream		Amount of recovered salicylate decr. proportionately as compared to above	

Table 8a (con't). Summary of Dermal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Sodium Salicylate, TEA-salicylate, Methyl Salicylate and Ethylhexyl (Octyl) Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		TEA-SALICYLATE - continued		
male and female Beagle dogs		Application to the shaved knee	23.7, 0.0039, and 0.001 µmol/g ^{3}H-TEA and 34.4, 0.061, and 0.002 µmol/g salicylate in the application site, synovial fluid, and serum	
6 arthritic human males	10 g	Cream massaged into a 25-30 cm^2 area over one knee	Synovial fluid, blood, and urine salicylate conc. were 0.16, 0.03, and 0.02 µg/ml after 1 h and 0.25, 0.08, and 0.18 µg/ml after 2 h	Rabinowitz et al., 1982
10 arthritic human males	10%	Massaged in for 60 min	Synovial fluid, blood, and urine salicylate conc. were 0.0011, 0.0002, and 0.0001 µmol/g for 6 patients not on bedrest and 0.0014, 0.0011, and 0.0020 µmol/g for 4 bedrest patients	Rabinowitz and Baker, 1984
humans/6 per sex	10%	Two 5 g applications to a 10 cm^2 area of the anterior thigh	No unchanged TEA-Salicylate or SA in the serum; 1.8 and 9.1 mg unchanged SA and SUA in the urine Total SA recovered was 6.9 mg; 1.4% recovered in the urine	Morra et al., 1996
		METHYL SALICYLATE (MS)		
Landrace pig skin	0.1-0.75 mg/ml	Absorption measured using ear skin	The penetration rate was approx. 0.125-0.6 mg/cm^2/h for 0.1-0.75 mg/ml	Loveday, 1961
hairless mouse skin	5.2 mg in 2 cm x 2 cm plaster	Plasters with the ingredient ± menthol and camphor topically applied	*In vitro* hydrolysis of MS to SA was linear; SA formation was inhibited by menthol and camphor in a dose-dependent manner	Yano et al., 1991
male and female guinea pig skin	5 µg/cm^2	Applied to viable and non-viable skin using flow-through diffusion cells	No sig. difference in absorption through viable and non-viable skin; at 24 h, 55 and 56% and 47 and 50% of applied dose absorbed was through male and female viable and non-viable skin Metabolism was different in male and female and viable and non-viable skin	Boehnlein et al., 1994
hairless mouse skin	1%, pH 4.0	0.95 cm^2 exposed using a glass flow-through diffusion cell system	Penetration flux decr. after 4 h; 17 µmol SA penetrated after 10 h A lower conc. resulted in a lower flux and more metabolized MS	Higo et al., 1995
male Wistar rats	10-28.3%	Application was made for 2 h to 9.625 cm^2 of depilated abdominal skin	MS was primarily converted to SA during transport through the skin Plasma MS SA ranged from 25-50 and 200-325 µg/g	Megwa et al., 1995
hairless mice	8.47 µCi (3.54 mg)	Applied to back	High levels of radioactivity found at the test site 1 h after application, peaking at 4 h; slight radioactivity seen at adjacent sites	Maruta et al., 1977
female hairless HRS/J (hr) mice	5.2 mg in 2 cm x 2 cm plaster	A plaster sheet was applied to dorsal skin ± menthol or camphor for 1, 3, or 6 h	The 1 h dermal conc. of MS and SA was 0.64 and 0.49 µmol/g, and the 6 h conc. were 0.29 and 0.22µmol/g Menthol and camphor incr. the 1 h values to 1.79 and 0.39 µmol/g	Yano et al., 1991
male SD rats	soln w/5% ethanol, pH 2, 3, 6, or 8	The tails were immersed in solution	The total amount absorbed at pH 2, 3, 6, and 8 was 1.56, 0.76, 1.77, and 1.57 µg/mm^2/h	Siddiqi and Ritschel, 1972
5-22 human males	20% in 80% anhydrous lanolin (1), 60% anhydrous lanolin and 20% menthol (2), or 60% of special aq. base (3)	10 g of was rubbed in to the skin of the chest, abdomen, and thigh	Mean salicylate excretion of ointments 1, 2, and 3 was 41.6, 55.1, and 47.5 mg In 8 subjects w/better cutaneous absorption than average (dark-complexioned subjects), 64.6, 101.3, and 103.1mg salicylate was excreted with ointment 1, 2, and 3	Beutner et al., 1943

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#/Species	Exposure Concentration	Application Site	Absorption	Reference
		METHYL SALICYLATE (MS) - continued		
human	Hydrous - 6 ml and 3 ml water Anhydrous - 6 ml	Application to the forearm under a 1 x 5 x 10 cm plastic cell for 16 h; test article was applied w/a 5 x 10 cm sponge	Urinary excretion was 8.6 and 2.7 mol/100 cm^2/h w/hydrous and anhydrous exposure; steady-state was reached at approx. 6 h	Wurster and Kramer, 1961
		Application for 2 h to defatted and nondefatted skin on 100 cm^2 of forearm	Defatting of skin decr. total salicylate absorption by 27%	
6 humans/gp	35.0 mg/sheet	Single or six 12-h applications of 10 sheets	Single application: serum free SA peaked at 8 h after dose initiation; greatest total SA concentration occured at 12 h Repeated applications: no free SA found 12 h after each application	Maruta et al., 1977
5 humans	12-50%	Application of 5 g was made under an occlusive patch for 10 h to a 50 cm^2 area of the forearm in a Latin Square design; a small portion was rubbed in and the rest was spread	Skin permeability coefficients ranged from 1.0-1.9 cm/h The amount of salicylate absorbed from each product ranged from 12-20%, and the estimated steady-state salicylate conc. ranged from 2.5-7.6 mg/l	Roberts et al., 1982
4 humans	25%	Application also made to the abdomen, instep, heel, and plantar region	Cumulative urinary recovery was greatest from application to the abdomen, followed by the forearm, instep, heel, then plantar region	
2 male and 4 female humans	1%	Application as a metered aerosol to forearms (also contained 5% each ethyl and 2-hydroxyethyl salicylate)	Methyl Salicylate (MS) was absorbed faster than ethyl salicylate, but the blood conc. of ethyl salicylate was greater MS in plasma peaked at 20 min	Collins et al., 1984
6 human males	5 g	Application was made to the back and chest and subjects were exposed to heat, exercise, or both for 6 h	Exercise and/or heat incr. plasma total salicylate conc. and urinary SUA Plasma salicylate conc. peaked at 2 h under all conditions	Danon et al., 1986
10 humans	0.03 g/l	20 min bath	Mean plasma salicylate concentrations were 452.6 and 116.6 ng/ml after 1 and 6 h; 5.08, 0.71, and 0.97 mg SUA excreted at 0-12, 12-24, and 24-48 h	Pratzel et al., 1990
humans/6 per sex	12.5%	5 g applied under a non-occlusive patch twice daily for 4 days to 10 cm^2 area of the anterior thigh	No unchanged MS was detected in serum or urine; serum SA ranged from 0.3-0.9 and 2-6 mg/l at 1 h and on day 4 and urinary max. SA and SUA conc. were 15.6 and 491.9 mg/l SA recovered on days 1, 2, 3, and 4 was 15.5, 22.0, 22.4,and 22.2%	Morra et al., 1996
		ETHYLHEXYL (OCTYL) SALICYLATE		
4 female human subjects	3% in o/w emulsion gel or petroleum jelly	Application made to a 100 cm^2 area of the back; sites wiped after 30 min and 2 and 6 h - 15 tape strippings	Max. conc. reached after 30 min; approx 37% of Ethylhexyl (Octyl) Salicylate from the o/w gel and 10% from pet. jelly found in tape strips 1-5 Before wiping, SPF values were 14.2 and 5.4 for the gel and the jelly; values decr. by a factor of 2.2 after wiping	Treffel and Gabard, 1996
		Using a Franz cell, 2.26 and 2.52 mg/cm^2 in gel and jelly applied to a 1.76 cm^2	0.94, 2.13, 1.54, and 7.29% of the dose from the gel and 1.81, 0.60, 1.97, and 1.96% of the dose from the jelly was recovered after 2 min, 30 min, 2 h, and 6 h; no to very little	

Table 8b. Summary of Oral Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Magnesium Salicylate, Sodium Salicylate, and Methyl Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA)		
5 gravid Wistar rats	0.2%	Fed treated diet on days 8-14 on day of gestation and then killed	Greatest SA conc. was in the serum (115.96 µg/ml) and lowest in the brain (4.14 µg/g) Fetal and amniotic conc. were 13.86 µg/g and 12.35 µg/ml	Tanaka et al., 1973a
5 gravid Wistar rats	150 mg/kg	Dosed daily on days 8-14 or given one dose on day 14 of gestation and killed 3 h after final dose	After single and multiple doses, the greatest SA conc. was in the serum (246.56 and 221.28 µg/ml) and the lowest was in the brain (23.82 and 24.86 µg/g) After single and multiple doses, fetal conc. were 55.83 and 62.48 µg/g and amniotic fluid conc. were 39.41 and 62.29 µg/ml	Tanaka et al., 1973b
male Fischer 344 rats	5, 50, or 500 mg/kg in corn oil/ethanol (4:1)	3, 12, and 25 mos old animals were given a single dose and killed after 96 h	All 3 mos old animals died and two 25 mos old animals were killed due to toxic effects of 500 mg/kg SA Almost all radioactivity was excreted in the urine; excretion was complete by 24 h in 3 and 25 mos and by 48 h in 12 mos old animals in animals given 5 mg/kg and by 48 h in all animals given 50 mg/kg The urinary metabolite profile was affected by age and dose	McMahon et al., 1990
4 male humans		Given orally as the free acid or sodium salt	Urinary pH ranged from 5.0-8.5 Amount of free SA, salicyluric acid, gentisic acid, and –OH and –COOH glycuronate conjugates recovered was 10-85, 0-50, ≤1, and 12-30 and 0-10%; total recovery was 85-95%	Alpen et al., 1951
6 female humans	66 µmol		Mean urinary recovery was 80% in 24 h	Janssen et al., 1996
7 male subjects	325 mg aspirin/ tablet	3 tablets were ingested	Salicylate elimination became log-linear between 6-9 h Mean conc. ratio of SA (semen/plasma) was 14.6	Kershaw et al., 1987
		MAGNESIUM SALICYLATE		
4 female beagle-type mongrel dogs	in 2tablet forms or as a soln	Animals were given 200 and 25 ml of water 30 min prior to and immediately following dosing	No difference between administration in tablet versus soln form C_{max} and t_{max} were 117-119 µg/ml and 1.0-1.6 h Bioavailability was 101 and 86% w/the tablets and 100% w/the soln	Alam et al., 1981
18 human males	481 mg SA equiv	Single oral dose was given w/240 ml water	The greatest plasma SA conc. was seen after 1.5 h (36.5 µg/ml) and the greatest urine salicylurate conc. occurred at 0-12 h (393 mg); in 24 h, 68.4% of the dose was excreted as salicylurate Plasma C_{max} and t_{max} were 1.44 µg/ml and 1.44 h	Mason, 1980
		SODIUM SALICYLATE		
10 gravid rats	500 mg/kg SA equiv	Given on day 11 of gestation in 2% methyl-cellullose	After 20 and 60 min, 296 and 316 mg/l free salicylate was found in the plasma and 38 and 52 mg/l were found in the brain	Davison et al., 1961
gravid Wistar rats	500 mg/kg	Some animals were pretreated w/benzoic acid; animals were killed 3, 6, 12, or 24 h after dosing	W/out pretreatment, the greatest free salicylate conc. was seen after 3 h; the 3 h salicylate conc. was 450 and 0.25 µg/ml in maternal serum and the fetus W/pretreatment, the max, conc in maternal serum was 475 µg/ml at 6 h and in the fetus was 0.26 µg/mg at 6 h	Kimmel et al., 1971
4 NZW rabbits	44 mg/kg	Single dose	SA was rapidly excreted in urine; more than 50% of the dose was SA and 4% was salicyluric acid; total recovery was 79%	Short et al., 1991

Table 8b (con't). Summary of Oral Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid, Magnesium Salicylate, Sodium Salicylate, and Methyl Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SODIUM SALICYLATE - continued		
human male	579.7 mg	Single dose	12.7% of the dose was excreted as SA w/in 96 h	Farid et al., 1975
44 male and 78 female black humans	1 g	Single oral dose	Males excreted more or the dose as SA glucuronide while females excreted more salicyluric acid	Emudianughe et al., 1986
black Nigerian humans/7 per sex	1 g SA as SS	Single dose	Males and females excreted 48.72 and 53.63% of the total dose in 12 h and excreted 2.83 and 6.13% as free SA Compared to females, males excreted sig. less of the dose as free SA and salicyluric acid and significantly more as salicylic acid acyl glucuronide	Emudianughe, 1988
5 human males	3 g SA as SS	Single dose in 400 ml water	Mean total recovery was 98% of the dose; 13, 48, 20, 12, and 3.9% was SA, salicyluric acid, salicyl phenolic glucuronide, and gentisuric acid	Shen et al., 1991
humans/6 per sex	9 mg/kg	Given in 200 ml water on days corresponding to days 2, 7, 14, 20, and 25 of the menstrual cycle Given a 2 min iv infusion 5 mos after the last dose	Mean kinetic values were similar w/oral and i.v. dosing W/the exception of t_{max}, kinetic values were similar for males and females; t_{max} was 24-34 min for males and 37-60 min for females Plasma C_{max} was 65.8-71.0 for males and 55.2-63.7 for females No sig. difference in salicylate distribution was seen on the different days	Miaskiewicz et al., 1982
22 human males, ages 30-85	600 mg	Single dose	Age had a minor influence on salicylate disposition SA was detected in the plasma of all subjects at 10-30 min; none was detected in 14 subjects at 24 h Urinary recovery of the total dose was 95% at 48 h, w/80% of the dose excreted as SUA and only 5% as unchanged SA SA and salicyluric acid C_{max} were 41.6-81.1 and 1.6-4.8 µg/ml Creatinine clearance was 58.8-168.8 ml/min and sig. decr. w/age	Abdallah et al., 1991
4 human males	650 mg	Given in 2 tablets 4x/day for 3 days	Serum and semen salicylate conc. were 21-170 and 3-33 mg/l 6 h after the last dose	Porat-Soldin and Soldin, 1992
human male	1 g SA as SS	Once, urine was kept acidic and once it was kept alkaline	Acidic: SA had a renal clearance of 0.16 ml/min and SA and its metabolites had terminal $t_{1/2}$ of 3 h; approx. 85% of the dose was excreted, primarily as salicyluric acid (68.7%); only 0.6% was unchanged SA Basic: SA had a renal clearance of 9.0 ml/min and a terminal $t_{1/2}$ of 2.6 h; approx. 91% of the dose was excreted, primarily as salicyluric acid (58.3%); 22.2% was unchanged SA	Vree et al., 1994a; 1994b
		METHYL SALICYLATE		
10 rats	500 mg/kg SA equiv	In 2% methylcellulose	After 20 and 60 min, 217 ad 278 mg/l free salicylate was found in the plasma and 8 and 42 mg/l were found in the brain	Davison et al., 1961
4 male and 2 female humans	0.42 ml		Mean Methyl and free salicylate values were 4.9 and 7.9 mg/l after 15 min and 2.8 and 10.5 mg/l after 90 min	Davison et al., 1961

Table 8c. Summary of Oral Mucosal Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID		
male golden hamsters	2% in various vehicles	Ointment was placed on the inside cheek	The blood SA conc. peaked at 70 µg/ml after 30 min w/a hydrophilic base, at 100 µg/ml after 1 h w/an absorption ointment, at 35 µg/ml after 3 h w/PEG ointment, and at 20 µg/ml after 3 h w/white petrolatum	Tanaka et al., 1980
male golden hamsters	pH 3, 4, and 7, w/out and w/surfactants	Absorption in the keratinized mucosa of the cheek pouch ± pretreatment with sodium lauryl sulfate and other surfactants	After 1 h, absorption of SA alone was 49.8 and 0.2% at pH 3 and 7 Sodium lauryl sulfate did not affect absorption at lower pH, but at pH 7, it sig. incr. absorption of SA to 8%; cetylpyridinium chloride and polysorbate-80 decr. SA absorption at the lower pHs, while sodium taurocholate did not affect absorption	Kurosaki et al., 1988
male golden hamsters	15 µmol/0.5 ml/kg, pH 3	Application was made to the oral mucosa using a cell system	Plasma C_{max} occurred at 45, 60, 120, and 180 min in the sublingual mucosa, ventral surface of the tongue, cheek pouch mucosa, and dorsum of the tongue; C_{max} of the sublingual mucosa was approx. 4.5 x greater than that in the dorsum of the tongue	Kurosaki et al., 1991

Table 8d. Summary of Parenteral Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid and Sodium Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SALICYLIC ACID (SA)		
dogs	1 g	i.v. in sodium bicarbonate	>90% of the dose was recovered in the urine; 50% as unchanged SA, 25% as glycuronates, 10% as salicyluric acid, and as 4-5% gentisic acid	Alpen et al., 1951
gravid SD rats	300 mg/kg	s.c.; animals were killed after 1 h	4.06% injected ^{14}C dose/dry wt fetal tissue	Koshakji and Schulert, 1973
4 gravid Suffolk or Suffolk-Dorset ewes		i.v. at 0 and 180 min w/SA and acetylsalicylic acid on day >137 of gestation	SA and acetylsalicylic acid crossed the placenta; equilibrium was reached at approx 40 min Mean SA clearance was 358 ml/min	Thiessen et al., 1984
male Fischer 344 rats	5 or 50 mg/kg	3 and 25 mos animals dosed i.v. in an Emulphor:ethanol:water (4:1:1) soln	At 5 and 50 mg/kg, plasma salicylate conc. were 17-28 and 100-120 µg/ml in both groups $t_{1/2}$s in 3 mos olds were 4.08 and 30.1 h and in 25 mos olds were 21.3 and 21.9 h w/5 and 50 mg/kg No SA metabolites were detected in the urine	McMahon et al., 1990
perfused rat liver			Hepatic metabolism of SA was negligible during a single pass	Shetty et al., 1994
humans		i.v.	89.9% recovered in the urine after 4 h	Feldmann and Maibach, 1970

Table 8d (con't). Summary of Parenteral Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid and Sodium Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
			SODIUM SALICYLATE (SS)	
gravid rabbits	1 or 1.5 g/kg	Single s.c. dose on day 30 of gestation	The maternal serum salicylate and pooled fetal serum conc. were 0.58 and 0.37 mg/ml in the animal given 1 g/kg and 0.75 and 0.45-0.62 mg/ml in the animal given 1.5 g/kg	Jackson, 1948
3-5 non-gravid A/Jax mice and gravid A/Jax and CBA mice/gp	0.1 ml/20 g	Single i.m. dose on day 14 of gestation and the animals were killed after 30 or 240 min or on day 17 of gestation and the animals were killed after 30-480	Blood radioactivity content was greater in non-gravid than gravid animals; in gravid animals, the content was generally greater in CBA than A/Jax mice on day 14 of gestation; on day 17, a strain difference was not seen; on both days, fetal radioactivity was initially greater in CBA mice	Eriksson and Larsson, 1971
gravid A/Jax mice	3 mg/20 g	Dosed on days 15-16 of gestation w/non-radioactive SS and w/radioactive SS on day 17, and killed 30-240 min after the last dose	Pretreatment w/non-radioactive SS incr. the variability of radioactivity in the blood	
rabbits	4 g/110 ml water	Animals dosed i.v.	$t_{1/2}$ was 1.5-4 h	Schuppli et al., 1972
6 rats or 6 ferrets	125 or 400 mg/kg	Single s.c. dose	W/125 and 400 mg/kg, blood salicylate conc. were 30 and 54 mg% in rats and 28 and 54.4 mg% in ferrets after 1 h	Gulamhusein et al., 1980
ıle and female SD rats (varying ages)	62 µmol/kg	Dosed i.v.	SA was the only compound found in the serum of dosed animals; urinary excretion of SA and SUA was similar for males and females Plasma clearances for male and female 1, 3, 8-9, 14-15, and 56-60 wk old animals were 22.0 and 25.0, 44.0 and 54.0, 23.3 and 13.8, 18.6, and 8.9, and 13.5 and 7.9 ml/kg/h; sig. differences were seen between males and females that were 8-9, 14-15, and 56-60 wks old and the values of 3 wk old animals were sig. incr. compared to all others Plasma $t_{1/2}$s for these animals were 13.9 and 12.0, 2.5 and 2.7, 6.6 and 7.3, 7.1 and 11.9, and 10.4 and 15.7 h; sig. differences were seen between 14-15 wk old males and females and the values of 3 wk old animals were sig. decr. Plasma SA conc. for these animals were 125-150 and 100-150, 50-113 and 50-81, 144-209 and 250-306, 125-250 and 159-388, and 188-269 and 206-356 nmol/ml	Varma and Yue, 1984
non- and gravid Wistar ST rats	10 mg/kg	Dosed i.v. (on day 20 of gestation for gravid animals)	Serum salicylate conc. were sig. decr. in gravid compared to non-gravid animals; serum $t_{1/2}$s were similar Fetal serum salicylate conc. were similar to maternal values; avg. values were 34.3, 21.7, and 22.5 µg/ml for non-gravid, gravid, and fetal animals Serum protein binding of salicylate was sig. decr. in gravid animals	Yoshikawa et al., 1984
5 non- and 5 gravid Wistar rats			The blood-to-plasma conc. ratios of SS from pooled blood to which non- and radioactive SS was added were 0.74 and 0.60 for gravid and non-gravid animals	
3-9 gravid SD rats/gp	15-500 mg/kg	Single i.v. dose on day 8 of gestation	After 1 min, 15, 50, 100, 200, and 500 mg/kg produced peak plasma conc. of 100, 300, 600, 900, and 1800 µg/ml; behavior of the 15 and 50 mg/kg doses was linear while that of 100-500 mg/kg was non-linear	Gabrielsson et al., 1985

Table 8d (con't). Summary of Parenteral Absorption, Distribution, Metabolism, and Excretion Studies for Salicylic Acid and Sodium Salicylate

#/Species	Exposure Concentration	Application Site	Absorption	Reference
		SODIUM SALICYLATE (SS) - continued		
12-14 gravid SD rats	1 or 2 mg/h	Constant infusion on days 6-13 of gestation	Plasma conc. peaked on days 6 and 8 of at approx. 110 µg/ml (range of 50-110 µg/ml) in animals given 1 mg/h and on day 8 at approx. 240 µg/ml (range 150-240 µg/ml) in animals given 2 mg/h	Gabrielsson et al., 1985
5 non- and 5 gravid hooded Wistar rats	50 mg/kg SA equiv	Single i.v. dose (on day 20 of gestation for gravid animals)	Absolute body clearance of salicylate was similar for both groups, by the absolute aVd was sig. incr. in gravid animals; normalized values indicated a sig. decr. in clearance and a slight incr. in aVd; $t_{1/2}$ was sig. incr. in gravid animals Gravid animals excreted less of the given dose, and the metabolic profile was changed Salicylate serum protein binding was decr. in gravid animals	Dean et al., 1989
gravid SD rats	150 mg/kg/day	Constant-rate i.v. infusion on days 6-13 of gestation	Blood salicylate conc. were 112-141 µg/ml (mean 120) on days 7-13 of gestation	Bergman et al., 1990
4 NZW rabbits	44 mg/kg	Single i.v. dose	SA was rapidly excreted in the urine, w/slightly >50% of the dose as SA and 4% as SUA; total recovery was 85.8%	Short et al., 1991
humans	250 mg	Dosed i.v.	83.8-94.5% of the dose was recovered in the urine in 24 h	Wurster and Kramer, 1961

INFLUENCE OF VEHICLES/ADDITIVES ON ABSORPTION

The majority of these studies have been described previously.

Salicylic Acid

In vitro, penetration of Salicylic Acid through human leg and breast skin was greatest from a lanolin, Plastibase®, and Hydrophilic Plastibase® (Squibb) vehicle, moderate from a carbowax base, and minimal from petrolatum (Flesch et al., 1955).

Absorption of Salicylic Acid from four vehicles, the oleaginous base petrolatum USP XV, the hydrophilic base petrolatum USP XV with water, the o/w base hydrophilic ointment USP XV, and the water-soluble base PEG ointment USP XV, was compared using rabbits (Stolar et al., 1960). The greatest absorption was observed with the hydrophilic base; negligible absorption was seen with the PEG ointment.

In a study using rabbits in which DMSO was added to four vehicles containing Salicylic Acid, DMSO increased the dermal absorption of Salicylic Acid from hydrophilic ointment USP XVII and hydrophilic petrolatum USP XVII when compared to absorption of Salicylic Acid from these bases without the addition of DMSO (Stelzer et al., 1969). It did not affect absorption of Salicylic Acid when added to PEG ointment or steareth-20 gel. The 10% Salicylic Acid was completely solubilized by the DMSO and surfactant added to the ointment. Marcus et al. (1970) also examined the effect of DMSO on absorption using rabbits. DMSO increased blood salicylate concentration when compared to hydrophilic ointment USP XVII without DMSO.

Yankell (1972) reported that, using guinea pigs, absorption of Salicylic Acid was greater from an ethanol-vehicle than an aq. vehicle.

In the study performed by Washitake et al. (1975) using a recirculation apparatus to examine the percutaneous absorption of Salicylic Acid from four "oily" vehicles, the amount of Salicylic Acid absorbed decreased as the affinity of drug to vehicle increased.

The effect of nonionic surfactants on the percutaneous absorption of Salicylic Acid was also examined using rabbits (Shen et al., 1976).

Salicylic Acid was completely solubilized by the DMSO and surfactants. Percutaneous absorption was significantly increased with the addition of sorbitan palmitate, sorbitan trioleate, poloxamer 182, poloxamer 231, laureth-4, oleth-2, or PEG-8 stearate to ointment containing Salicylic Acid and DMSO. Mixed surfactants of varying hydrophilic-lipophilic balance (HLB) values resulted in a prolonged percutaneous absorption effect.

Salicylic Acid, 2% in PEG or an emulsified ointment, was applied in a thin layer, 0.5 mm, to a 60 cm^2 area on the inner forearm of human subjects (Zecchi et al., 1978). The residual Salicylic Acid concentration was measured at various times for up to 4 h. The permeability coefficient was 0.0917 and 2.53 $cm \cdot sec \cdot 10^6$ with the PEG and emulsified vehicles, respectively.

In a clinical study in which Salicylic Acid was applied in a PEG-8 solution or a hydrophilic ointment, minimal systemic absorption occurred with the PEG solution; this was attributed to "the formation of a glycol-salicylate complex resulting in a molecule too large to pass the stratum corneum" (Birmingham et al., 1979). With the ointment, Salicylic Acid was not found in the blood but was found in tape-stripped skin.

In a study in which Salicylic Acid was applied to the oral mucous membrane of the hamster cheek pouch, the base affected absorption (Tanaka et al., 1980). More Salicylic Acid was absorbed from "absorption" and hydrophilic bases as compared to PEG and petrolatum bases.

The effect of polar lipids on the transport of lipophilic molecules through the human epidermis was examined (Cooper, 1984). The addition of small amounts of fatty acids of alcohols to a formulation can increase the transport of Salicylic Acid by an order of magnitude.

In a study using a membrane system, a greater percentage of the Salicylic Acid dose penetrated the membrane layers from a Aqueous emulsion compared to a vaseline base (Neubert et al., 1990).

Bioavailability of Salicylic Acid was determined in a clinical study using a hydroalcoholic vehicle (63% water/35% ethanol) or a cream (80% water/18% cosmetic excipient mixture) (Davis et al., 1997). C_{max} and t_{max} were greater and faster, respectively, with the hydroalcoholic vehicle.

Ethylhexyl Salicylate

In a clinical study, a greater amount of Ethylhexyl (Octyl) Salicylate absorbed into skin using an o/w emulsion gel compared to using petrolatum jelly (Treffel and Gabard, 1996).

Methyl Salicylate

Dermal absorption of Methyl Salicylate from three different vehicles was compared in a clinical study (Beutner et al., 1943). Menthol seemed to enhance absorption. Yano et al. (1991) found that the addition of menthol and camphor to Methyl Salicylate increased absorption.

Sodium Salicylate

Absorption of Sodium Salicylate from four vehicles, the oleaginous base petrolatum USP XV, the hydrophilic base petrolatum USP XV with water, the o/w base hydrophilic ointment USP XV, and the water-soluble base PEG ointment USP XV, was compared using rabbits (Stolar et al., 1960). The greatest absorption was observed with the hydrophilic base; negligible absorption was seen with the PEG ointment.

In a study using rabbits in which DMSO was added to two vehicles containing 11.6% Sodium Salicylate, DMSO significantly decreased the dermal absorption of Sodium Salicylate from hydrophilic ointment USP XVII when compared to absorption of Sodium Salicylate from the ointment without the addition of DMSO (Stelzer et al., 1969). It did not affect absorption of Sodium Salicylate when added to hydrophilic petrolatum.

The effect of nonionic surfactants on the percutaneous absorption of 11.6% Sodium Salicylate was examined using New Zealand white rabbits (Shen et al., 1976). Approximately one-third of the 11.6% Sodium Salicylate was solubilized by the DMSO and surfactant added to the ointment. Percutaneous absorption was significantly increased with the addition of sorbitan laurate, sorbitan palmitate, or poloxamer 182 to the ointment containing Sodium Salicylate and DMSO. Mixed surfactants of varying HLB values resulted in a prolonged percutaneous absorption effect.

TEA-Salicylate

The *in vitro* release of TEA-Salicylate from a hydrophilic and a "water-washable" base and from two commercial products was determined using a

Franz diffusion cell assembly with 176 mm^2 surface area (Babar et al., 1991). The effect of 5-15% ethanol, propylene glycol, PEG-400, or DMSO, of 1-3% polysorbate-80, and of 2-5% urea on the release from each base was also determined. The ointments made with the hydrophilic and water-washable bases each contained 10% TEA-Salicylate. After 2.5 h, 7.4 and 12.6% TEA-Salicylate was released from the commercial products, and 13.3 and 15.3% was released from the hydrophilic and water-washable bases, respectively.

The greatest release from the hydrophilic base, 35.1%, was observed with the addition of 10% ethanol. With the addition of 5% DMSO, only 8.2% TEA-Salicylate was released in 2.5 h. The greatest release with the water-washable base, 20.3%, occurred with the addition of 3% polysorbate-80. With the addition of 10% ethanol, only 7.9% was released. With the hydrophilic base, the greatest first-order release-rate constant (Kr), diffusion coefficient (D), and permeability coefficient (P), and the lowest K_p, were observed with the addition of 10% ethanol. The lowest Kr, D, and P and the greatest K_p was observed, when compared to the hydrophilic ointment plus additives, with the commercial formulation. With the water-washable base, the greatest Kr was observed with the addition of 15% PEG-400 and the greatest D and P and the lowest K_p were observed with polysorbate-80. The lowest Kr, D, and P and the greatest K_p were seen with the addition of 15% ethanol to the water-washable ointment.

PENETRATION ENHANCEMENT

Salicylic Acid

In an *in vitro* study, a negative corium spot test was obtained with vitamin A alone after 24 h (Flesch et al., 1955). However, with the addition of 10% Salicylic Acid, the test was positive after 3 h of incubation.

The penetration of 0.1% tritiated triamcinolone acetonide from 60% ethanolic solution alone and with 10% Salicylic Acid was compared *in vitro* using sheets of human epidermis obtained from abdominal skin (Polano and Ponec, 1976). The penetration of 10% Salicylic Acid was also determined. Salicylic Acid "greatly increased" the penetration of triamcinolone acetonide. The penetration of Salicylic Acid peaked at ~4 h (>150 µg penetrated), while the penetration of triamcinolone acetonide peaked at ~25 h; however, enhance penetration of triamcinolone acetonide persisted.

The influence of Salicylic Acid on the epidermis was then evaluated by incubating the epidermal sheets with water, 60% ethanol, and 10% Salicylic Acid in 60% ethanol for 2 h, and then determining the penetration of 1% methyl nicotinate (which penetrates the skin rapidly). There was no detectable change in the penetration of methyl nicotinate regardless of pretreatment.

Salicylic Acid is reported to enhance the dermal permeation of ammoniated mercury (Pascher, 1978).

Female rhesus monkeys were used to determine the effect of Salicylic Acid on the dermal penetration of hydrocortisone (Wester et al., 1978). The ventral forearm of each animal was lightly shaved and 13.3 µg/cm^2 ^{14}C-hydrocortisone (5 µCi) in either acetone (five animals) or a formulation of 60% ethanol, 5% propylene glycol, 5% glycerin, and 30% water (EPGW) (four animals) was applied to a 6 cm^2 area without occlusion. Hydrocortisone was also applied with Salicylic Acid (five animals/group); doses of 13.3 and 133.3 µg/cm^2 were used with acetone as the vehicle and of 133.3 µg/cm^2 with EPGW as the vehicle. (The concentrations used in the study were determined to be 0.8% hydrocortisone solution and 0.8 or 8% Salicylic Acid solution.) The animals were secured in metabolic chairs for the first 24 h; the test solutions were then washed from the skin and the animals were returned to metabolic cages. Urine was collected for 5 days. When hydrocortisone was applied in acetone alone or with 13.3 or 133.3 µg/cm^2 Salicylic Acid, 1.37 ± 0.97, 1.19 ± 0.43, and 1.14 ± 0.25% of the dose, respectively, was excreted in the urine. When applied in EPGW alone or with 133.3 µg/cm^2 Salicylic Acid, 1.27 ± 0.52 and 0.96 ± 0.41% of the dose, respectively, was excreted. There was no statistically significant difference in the percutaneous absorption of hydrocortisone with or without the addition of Salicylic Acid; Salicylic Acid seemed to slightly decrease hydrocortisone absorption.

The effect of Salicylic Acid on the percutaneous absorption of DFV was determined using a group of six human subjects (Täuber et al., 1993). (Protocol described previously.) Compared to a formulation without Salicylic Acid, percutaneous absorption of DFV was not affected by the addition of Salicylic Acid. Also, it did not affect the concentration of cortisol in the urine or dehydro-

epiandrosterone in the plasma.

The effect of Salicylic Acid on the transdermal delivery of cyclosporin through abdominal skin of male hairless mice was determined *in vitro* (Wang et al., 1997). Salicylic Acid was added at concentrations of 0.1-5%. Salicylic Acid did not affect the transdermal absorption of cyclosporin though mouse skin.

SKIN EFFECTS

Salicylic Acid

The effect of Salicylic Acid on pathological epithelial proliferation was evaluated in an epidermal hyperplasia test using male Pirbright albino guinea pigs (Weirich et al., 1975). Hyperplasia was induced with hexadecane. A group of 15 animals were dosed dermally with 3% Salicylic Acid in 99% ethanol, one dose of 1 ml and then twice daily doses of 0.1 ml for 7 days, and a group of three animals were dosed with 1% w/w Salicylic Acid in a dimethylacetamide-acetone-ethanol mixture (DAE 244), 0.1 ml twice daily for 7 days; both test groups were dosed in conjunction with seven daily doses of 0.1 ml hexadecane. The site of application was a 5.31 cm^2 circular area on the back. Tissue biopsies were taken on day 11 with 3% and day 10 with 1% Salicylic Acid.

Salicylic Acid had an antihyperplastic effect. Salicylic Acid at 3% in ethanol reduced surface epithelial hyperplasia by 15%; it had no effect on proliferation of the deep epithelium. At 1% in DAE 244, Salicylic Acid reduced surface epithelial hyperplasia by 18% and also significantly reduced deep epithelial proliferation; the reduction in the deep epithelium was 10% compared to the effects seen with 3% Salicylic Acid. Total epithelial volume was reduced with 1% Salicylic Acid compared to DAE and hexadecane. The vehicle affected the keratolytic effect of Salicylic Acid.

Guinea pig skin was used to examine the keratolytic effect of Salicylic Acid (Huber and Christophers, 1977). The external ears and soles of the feet of dead guinea pigs were removed, and a 50% solution of Salicylic Acid in ether was applied. The tissue specimens were then incubated in humidity chambers for 10 h, after which time they were rinsed with ether and cryostat sections were prepared.

No difference was seen microscopically in the horny layer of treated and untreated samples. Application of mechanical stress, applied by moving the cover slip, caused the treated stratum corneum to break. In the control samples, the cells became elongated and flattened, but no cellular separation occurred. Upon stretching the stratum corneum, intercellular separation was constantly observed with the test samples, but never observed with the controls.

Epidermoplasia tests were conducted to determine the effect of Salicylic Acid on normal guinea pig skin (Weirich et al., 1978). Salicylic Acid, 1% in acetone/ethanol (50:50 w/w), was applied to the skin of three animals 20 times within a 4 wk period. The single dose volume was 200 µl/5.31 cm^2 and the single surface dose was 0.276 mg/cm^2. Skin biopsy samples were examined using epidermal pachometry and planimetry, and the mitosis rates in the basal epidermal layer was determined.

No irritation or degenerative changes were observed during the study. Salicylic Acid did not have an inhibitory effect on epidermopoiesis in normal guinea pig skin. It caused a significant thickening of the surface epithelium, a significant increase in the volume of deep and total epithelium, and a distinct but non-significant increase in the mitosis rate in the germinative zone of the epidermis. Some intracellular and interstitial edema or slight spongiosis was observed. No hyperkeratosis was seen, and most sections of the horny layer of the skin treated with Salicylic Acid were almost completely detached. A "definite increase" in the number of cells and cell layers was observed.

The effect of Salicylic Acid on the skin of female hairless rhinoceros mice was examined (Kligman and Kligman, 1979). Using eight animals per group, 100 µl of 1, 5, or 10% Salicylic Acid in an ethanol vehicle was applied to the entire dorsal trunk of each animal twice daily, 5 days per wk. Four animals per group were killed after 3 wks and four after 6 wks. Slight epidermal hyperplasia was observed with 10% Salicylic Acid. In all dose groups, a moderate reduction in the quantity of horny material within the psuedocomedones, which retained their shape, was seen, and the "core of the horny impaction often seemed empty as if the contents had been lost."

The effect of Salicylic Acid on the stratum corneum was determined by measuring turnover

time using the dansyl chloride fluorescence method (Takahashi et al., 1987). Occlusive patches of 5% dansyl chloride in white soft paraffin were applied to depilated skin on the backs of five guinea pigs for 24 h. One test site was then treated daily with 0.1 ml/4 cm^2 of 6% Salicylic Acid. An untreated site was used as a control.

Salicylic Acid significantly increased the rate of stratum corneum exfoliation as compared to the control; the mean turnover rate was 2.9 and 11.0 days for the test and control sites, respectively. Skin thickness was not affected by Salicylic Acid. Because the epidermis was not thickened or irritated, the authors concluded that Saclicylic Acid may act directly on the intercellular cement substance of the corneocytes.

OTOTOXICITY

Ototoxicity, manifesting as mild to moderate reversible hearing loss and tinnitus, is a reported side-effect of salicylates (Jung et al., 1993). Salicylates rapidly enter the cochlea after systemic administration. Hearing loss is bilaterally symmetric and may be flat or in the high frequencies. Recovery usually occurs 24-72 h after cessation of salicylates. According to these authors, age increases the risk of salicylate toxicity even at lower salicylate doses.

Sodium Salicylate

In a study to track the distribution of H^3-labeled Sodium Salicylate in the cochlea to better understand possible mechanisms of salicylate ototoxicity, Ishii et al. (1967) injected five albino guinea pigs i.v. or i.p. with a 50 mCi/27.5 mg) solution. The animals were killed at intervals ranging from 15 min to 13 h and the cochleas examined (Ishii et al., 1967). Fifteen min after i.v. dosing, the radioactivity was found primarily in the lumen of the vessels in the stria vascularis and spiral ligament. One h after i.p. injection, the radioactivity was still primarily in the stria vascularis and the spiral ligament, but some had diffused into the organ of Corti and Rosenthal's canal. Six and 13 h after i.p. injection, little and no radioactivity, respectively, was found. The authors concluded that the distribution was so rapid and widespread that the possibility that certain cells may be specifically susceptible to damage cannot be excluded.

Salicylate intoxication produced biochemical changes in endolymph and perilymph of the ear of cats (Silverstein et al., 1967). The electrical activity of the cochlea, recorded from the round window area, had an increase in threshold of 20-24 dBs 2-3 h after i.p. injection of 350 mg/kg Sodium Salicylate.

In guinea pigs that were given a single s.c. dose of Sodium Salicylate, the salicylate interfered with the cochlea's ability to generate a nerve evoked potential; this effect was reversible (Mitchell et al., 1973). A corresponding change in the ability of the cochlea to generate the alternating current cochlear potential was not seen. The effect of Sodium Salicylate was dependent on the blood salicylate concentration and, more importantly, the perilymph concentration.

Five monoaural chinchillas were injected i.m. with 400 mg/kg Sodium Salicylate, and auditory thresholds were measured 2 h after dosing and at regular intervals for 16 days (Woodford et al., 1978). Two h after dosing, the median temporary threshold $shift_{max}$ (TSS_{max}) was 21 dB at 8 kHz. The range of threshold shifts at all frequencies was 0-28 dB, and the time of TSS_{max} was variable but generally occurred 2-6 h after dosing. There was a tendency toward larger TSS at higher frequencies. Noise in conjunction with dosing did not exaggerate the results.

Dunkin-Hartley guinea pigs were given a single s.c. dose of 500 mg/kg Sodium Salicylate and killed 4 and 24 h after dosing or were given daily s.c. doses of 375 mg/kg Sodium Salicylate for 5-7 days and killed 24 h-6 wks after dosing, and the cochleas were examined (Douek et al., 1983). Effects were seen in the outer and inner hair cells after a single dose and after multiple doses.

Sodium Salicylate was added to cultures of postnatal cochlear explants to determine the ototoxic effect (Zheng and Gao, 1996). Sodium Salicylate dose-dependently induced spiral ganglion neuron death and degeneration of their peripheral neurites. It did not affect hair cells. Neuronal degeneration could be prevented by the addition of neurotrophins.

HEMORRHAGIC EFFECTS

Salicylic Acid

Five male Sprague-Dawley rats were fed a diet

containing 1.67 mmol Salicylic Acid per 100 g diet and five male ICR mice were fed a diet containing 6.68 mmol Salicylic Acid for 1 wk (Takahashi and Hiraga, 1985). Control animals were given untreated feed. The mean daily intake of Salicylic Acid was 1.48 and 13.7 mmol/kg for rats and mice, respectively. The prothrombin (PT) and kaolin-activated partial thromboplastin time (K-PTT) indices were not significantly different between the treated and control rats due to large variances. However, two of the treated rats had abnormal PT (<30%) and K-PTT (<45%) indices. In mice, the K-PTT was slightly decreased. The relative liver weights of mice, but not rats, were significantly increased compared to controls.

HEMOLYTIC EFFECTS

Methyl Salicylate

Erythrocytes from adult males (HRBC) and from sheep (SRBC) were incubated with Methyl Salicylate to determine the hemolytic effect (Murugesh et al., 1981). The numbers of cells treated were not stated. Methyl Salicylate, 0.004 ml, induced hemolysis in both HRBC and SRBC. Hemolysis increased with concentration and duration of incubation. Methyl Salicylate caused extensive membrane damage, probably due to its ability to decrease the surface tension of saline.

PHOTOPROTECTIVE EFFECTS

Ethylhexyl Salicylate

The phototoxic protection factor of a formulation containing 5% Ethylhexyl (Octyl) Salicylate, 7% octyl dimethyl PABA (padimate O), and 3% benzophenone-3 was determined using subjects with type I or type II skin (Lowe et al., 1987). In phase 1 of the study, 2 µl/cm^2 0.1% 8-methoxypsoralen (8-MOP) in isopropyl alcohol was applied to all test sites and allowed to dry for 15 min; 2 µl/cm^2 was then applied to half the test sites. After 15 min, the sites were irradiated with 0.1-0.8 J/cm^2 UVA; after 72 h, erythema was graded at all sites. In phase 2, 8-MOP was again applied and allowed to dry. Two µl/cm^2 of the formulation was applied to one site; after 15 min the sites were irradiated with 3-8 times the minimal phototoxic dose, with a UVA dose range of 0.4-4.3 J/cm^2.

The formulation containing 5% Ethylhexyl (Octyl) Salicylate had a mean phototoxic protection factor (ratio of the mean phototoxic dose for protected and unprotected skin) of 3.3; this was significantly increased compared to the vehicle.

ANTIMICROBIAL ACTIVITY

Salicylic Acid

The minimal inhibitory concentrations (MICs) of 0.5% Salicylic Acid against gram positive bacteria, gram negative bacteria, fungi and yeasts, and molds were 2000, 3000, 3000, and 5000 ppm, respectively (Kabara, 1984). Only undissociated Salicylic Acid is active, and it should be used as an antimicrobial preservative in the pH range 2-5. Salicylic Acid attacks the plasma membrane of bacteria and inhibits some enzyme systems.

CYTOTOXICITY

Salicylic Acid

The inhibitory effect of Salicylic Acid on HeLa cells, *B. subtilis*, and *E. coli* was examined (Sheu et al., 1975). The concentrations of Salicylic Acid needed for 50% growth inhibition were 1.8, 1, and 4 mM, respectively.

Kleinerman et al. (1981) reported Salicylic Acid enhanced spontaneous monocyte cytotoxicity.

Viljoen et al. (1995) found that Salicylic Acid at concentration ranges from 10^{-10} M to 10^{-2} M had no effect on plating efficiency of human prostatic carcinoma DU-145 cells, but that cell growth was inhibited at concentrations >10^{-8} M and completely inhibited at concentrations >10^{-4} M. Salicylic Acid increased [^{3}H]thymidine (^{3}H-TdR) incorporation, with a decrease in DNA synthesis, and inhibited protein synthesis as detected by [^{3}H]glycine incorporation.

In a cytotoxicity study, Salicylic Acid had NI_{50} values (concentration required to induce a 50% inhibition of neutral red uptake) of 16.9, 7.1, 16.6, and 14.9 mmol/l in MDCK (dog distal renal tubular cells), LLC-PK1 (pig renal proximal tubular cell), NRK (normal rat kidney, indefinite origin), and HepG2 (human hepatoma) cells, respectively (Noble et al., 1997). Salicylic Acid decreased the reduced glutathione (GSH) content in all renal cell lines, with the decrease in the NRK cells being concentration-dependent, and it increased the GSH content in the HepG2 cells.

Methyl Salicylate

The inhibitory effect of Methyl Salicylate on HeLa cells and *B. subtilis* was examined (Sheu et al., 1975). The concentrations of Methyl Salicylate needed for 50% growth inhibition were 2.8 and 6.5 mM, respectively.

Sodium Salicylate

Hial et al. (1977) reported that low concentrations ($\leq$ 0.5 mM) of Sodium Salicylate stimulated protein and nucleic acid synthesis while high concentrations ($\geq$ 1 mM) inhibited growth and protein and nucleic acid synthesis in human fibroblast and rat hepatoma cultures.

The effect of Sodium Salicylate on thiol content in the isolated liver was examined in order to determine toxicity (Nishihata et al., 1988). At concentrations <25 mM, Sodium Salicylate did not affect glucose release or thiol content. A slight but insignificant decrease in non-protein and protein thiol was observed at 50 mM, and an increase in glucose release was observed at "an early stage after perfusion." Glucose release was then at control values.

The effect of Sodium Salicylate on inducible nitric oxide synthase (iNOS) expression and function was examined using murine macrophage cells (RAW 234.7) (Amin et al., 1995). Sodium Salicylate had no significant effect on nitrite production at pharmacological concentrations (3 mM), but it significantly inhibited nitrite production at suprapharmacological concentrations (5 mM). However, the IC_{50} for nitrite accumulation was 20 mM. Pharmacological concentrations of Sodium Salicylate had no effect on the activity of cyclooxygenase-2. Immunoblot analysis of iNOS expression in the presence of Sodium Salicylate showed variable inhibition (0-35%). Pharmacological concentrations of Sodium Salicylate did not affect iNOS mRNA expression. The researchers stated that lower concentrations of Sodium Salicylate interfere with enzyme synthesis, while greater concentrations inhibit catalytic activity of iNOS.

Cultured rat cardiac fibroblasts were used to determine the effect of Sodium Salicylate on the inhibition of the induction of iNOS (Farivar et al., 1996). Sodium Salicylate inhibited cytokine-induced nitrite accumulation in a time- and dose-dependent manner, with an IC_{50} of 750 µmol/l. Sodium Salicylate was effective when added both before and after cytokine induction, and the effect was reversible. High-dose Sodium Salicylate pretreatment prevented cytokine-induced stimulation of PGE_2. Sodium Salicylate inhibited cytokine-induced iNOS mRNA levels but not iNOS enzymatic activity.

Farivar and Brecher (1996) further investigated the effect of Sodium Salicylate on the inhibition on iNOS induction. It was again found that Sodium Salicylate inhibited NOS 2 mRNA accumulation in a dose-dependent manner, and inhibition occurred with addition of Sodium Salicylate both before and after the addition of cytokines. Sodium Salicylate was able to reduce mRNA following prolonged induction by cytokines. Sodium Salicylate did not affect NOS 2 mRNA half-life, and it did not inhibit the induction of NF-κB or signal tranducers and activators of transcription-1 (STAT-1) by electrophoretic mobility shift assay (EMSA).

The ability of Sodium Salicylate to inhibit nitric oxide formation induced by IL-1β was evaluated using rat hepatocytes (Sakitani et al., 1997). Simultaneous addition of Sodium Salicylate with IL-1β inhibited nitrite production. Inhibition was also observed when Sodium Salicylate was added 1-3 h after IL-1β. Inhibition was dose-dependent; maximal and half-maximal concentrations were 20 and 7 mmol/l, respectively. Sodium Salicylate did not affect NF-κB activation or iNOS mRNA expression induced by IL-1β. Sodium Salicylate abolished the synthesis of iNOS protein.

Schwenger et al. (1997) found that Sodium Salicylate treatment was cytotoxic to normal human diploid FS-4 fibroblasts. A p38 kinase inhibitor suppressed the Sodium Salicylate-induced apoptosis. In a cytotoxicity study, Noble et al. (1997) reported that Sodium Salicylate had NI_{50} values of 20.6, 8.0, 21.2, and 9.0 mmol/l in MDCK, LLC-PK1, NRK, and HepG2 cells, respectively. Ekwall and Acosta (1982) found that Sodium Salicylate had a MIC of 1.0×10^4 µg/ml in HeLa cells, with an IC_{50} value of 3×10^{-2} mol/l with a 24 h incubation period. The concentration inducing lactate dehydrogenase (LDH)-release by 50% was 5×10^{-3} mol/l in primary rat hepatocyte cultures after 3 and 24 h incubation periods. Borel (1976) examined the effect of Sodium Salicylate on cell-mediated cytolysis in a system using C57BL/6 mouse spleen cells sensitized with allogeneic tumor cells. Sodium Salicylate did not inhibit, as compared to controls, the cytolytic interaction.

IMMUNOLOGIC EFFECTS

Salicylic Acid

Female Sprague-Dawley rats were used to determine the anti-inflammatory effects of Salicylic Acid, Salicylic Acid and nicotinic acid, Salicylic Acid and pyridyl-3-methanol, and an ester of pyridyl-3-methanol and Salicylic Acid (S-2063) in a carrageenin-induced edema test (Cekanova et al., 1974). The test compounds were given orally as a dose of 2 ml/100 g body wt in a 1% solution of carboxymethyl cellulose 30 min prior to injection of the carrageenin. Salicylic Acid had "significant anti-inflammatory effects". The anti-inflammatory effects of Salicylic Acid and nicotinic acid were additive, the effects of Salicylic Acid and pyridyl-3-methanol were less than that of Salicylic Acid and nicotinic acid, and the effects of S-2063 were similar to that of Salicylic Acid and pyridyl-3-methanol.

A single oral dose of 100 mg/kg Salicylic Acid reduced paw swelling in the arachidonic acid-potentiated and carrageenan-induced edema tests 9 and 36%, respectively, compared to controls (Smith et al., 1979). In 9 h sponge exudates in the rat, a single oral dose of 200 mg/kg Salicylic Acid inhibited prostaglandin-like activity and total leukocytes 83 and 43%, respectively, compared to controls. However, direct administration of 0.5 mg Salicylic Acid to the sponge only inhibited prostaglandin-like activity and total leukocytes 16 and 0%, respectively.

Methyl Salicylate

A rodent ear assay was performed using Methyl Salicylate to assess the inflammation response using ear thickness as a determinant (Patrick et al., 1985; 1987). A dose of 5 µl Methyl Salicylate was applied to the dorsal and ventral surfaces of the pinna of one ear of female ICR mice, and solvent was applied to the contralateral ear. Ear thickness was measured prior to application and at various times following application. The components of the inflammatory response were determined; histological evaluation was made at the time of maximum ear thickness, i.e. 20 min; trypan blue was used, leakage of ^{125}I-bovine serum albumen (^{125}I-BSA) was measured, and differences in temperature of the treated and untreated external ears were determined.

Undiluted Methyl Salicylate produced a maximum response at 30 min; doses of 2.5-7.5 mg produced maximum responses at 15 min. The ears returned to normal thickness after termination of dosing. Microscopically within 20 min, Methyl Salicylate produced rapid dilation of blood vessels, prominent vessels of the margin of the external ear, and moderate edema. These results were confirmed with trypan blue and ^{125}I-BSA. The temperature of the external ears treated with Methyl Salicylate increased rapidly and returned to normal within 20 min.

Normal human epidermal keratinocytes from female breast skin were used to examine cytokine production due to Methyl Salicylate (Wilmer et al., 1994). Methyl Salicylate, 500 µg/ml, did not induce IL-8, TNF-α, or granulocyte/macrophage colony-stimulating factor (GM-CSF).

Sodium Salicylate

Using male Swiss albino mice, s.c. injection of Sodium Salicylate at 100 mg/kg increased the serum concentration of interferon 210%, while a dose of 300 mg/kg decreased the serum concentration of interferon by 65% (Geber et al., 1975a; 1975b).

The effect of Sodium Salicylate on prostanoid synthesis and platelet aggregation was determined using female subjects (Rosenkranz et al., 1986). The subjects were given 52.6 mg/kg Sodium Salicylate daily for 8 days. Sodium Salicylate did not affect urinary excretion of prostaglandin E_2 (PGE_2), PGE-M, or 2,3-dinor-6-keto-$PGF_{1\alpha}$. It also did not affect platelet aggregation or thromboxane formation.

Male Wistar rats were used to examine the effect of Sodium Salicylate on *ex vivo* mucosal eicosanoid release and on ethanol-induced gastric damage (Peskar et al., 1988). Some animals were given 6.25-400 mg/kg Sodium Salicylate in 0.25% w/v carboxymethylcellulose orally 30 min prior to gastric instillation of 1.5 mol ethanol; the animals were killed after 5 min. A second set of animals was given 25-400 mg/kg Sodium Salicylate in carboxymethylcellulose without ethanol instillation and killed 30 min later, and a third set of animals was given a s.c. injection of 400 mg/kg aq. Sodium Salicylate and killed after 1 h.

Oral pretreatment with Sodium Salicylate prior to ethanol instillation dose-dependently inhibited the

stimulatory action of ethanol on gastric leukotriene C_4 (LTC_4) release, but PGE_2 and thromboxane B_2 (TXB_2) release were not altered. Release of 6-oxo-$PGF_{1\alpha}$ was increased; the increase was significant with 100 mg/kg Sodium Salicylate. In animals not given ethanol, Sodium Salicylate did not affect LTC_4, PGE_2, 6-oxo-$PGF_{1\alpha}$, or TXB_2 release, and s.c. administration had no significant effect on *ex vivo* gastric mucosal eicosanoid release.

Raghoebar et al. (1988) studied the association of Sodium Salicylate with leukocytes. The degree of cell association of salicylate with mononuclear leukocytes (MNLs) was approximately two times less than the amount of cells associated with polymorphonuclear leuocytes (PMNs). Association of Sodium Salicylate with PMNs is markedly enhanced when extracellular pH is decreased; the researchers stated that this suggests that passive nonionic diffusion is an important mechanism in cell association. Phorbol 12-myristate 13-acetate (PMA), 0.13 µM, increased the intracellular concentration of Sodium Salicylate at anti-inflammatory concentrations (1.5-2.1 mM Sodium Salicylate). Cell association of Sodium Salicylate with PMNs increased markedly in the presence of the metabolites SUA and gentisic acid.

The effect of Sodium Salicylate on neutrophil function was determined (Abramson et al., 1991). Sodium Salicylate inhibited neutrophil aggregation in response to stimuli that require signal transduction via a G protein, but it did not have an effect on stimuli that bypass receptor-G protein interaction. Sodium Salicylate inhibited the binding of GTPγS, a stable analog of GTP, to purified neutrophil membrane preparations. The researchers determined that Sodium Salicylate interacts with a G protein in the neutrophil plasmalemma and uncouples post-receptor signaling events.

The ability of Sodium Salicylate to inhibit stimulated neutrophil adhesion to epithelium was examined (Cronstein et al., 1994). Neutrophils were isolated from human whole blood, and human umbilical vein endothelial cells (HUVEC) were obtained by collagenase treatment fo fresh human umbilical cords. Sodium Salicylate, 5 mM, did not affect adhesion of unstimulated neutrophils, but it inhibited stimulated neutrophil adherence to epithelium (50% inhibition at 0.5 mM) in a concentration dependent manner. In examining the effect of Sodium Salicylate on the ATP concentration in resting and stimulated neutrophils, 1 mM markedly decreased neutrophil ATP concentration with incubation less than 1 h. A concentration-dependent decrease in ATP concentration was observed with a 10-min incubation period (50% decrease at 0.6 mM). Adenosine deaminase reversed the effect of Sodium Salicylate on stimulated adhesion to the endothelium. Therefore, the researchers theorize that Sodium Salicylate promoted the release of adenosine from cells and that the released adenosine inhibited the adhesion of stimulated neutrophils to the endothelium.

The effect of Sodium Salicylate on the expression of monocyte chemotactic protein-1 (MCP-1/JE) and interferon inducible protein-10 kD (IP-10) chemokines in stromal cells was determined as a function of concentration ranging from 0.5-40 mmol/L (Gautam et al., 1995). Sodium Salicylate inhibited induction of chemokine mRNA in bone marrow stromal cells, in a concentration-dependent manner, without affecting the viability of these cells. Maximum suppression of induction was seen at 40 mmol/L and moderate suppression at 20 mmol/L. The suppression of mRNA expression was not dependent on synthesis of new proteins. Sodium Salicylate did not affect mRNA stability. Activation of transcription factor nuclear factor-κB (NF-κB) was inhibited by Sodium Salicylate in a dose-dependent manner.

Pierce et al. (1996) studied the effect of Sodium Salicylate at concentrations ranging from 0-20 mM on the expression of adhesion molecules in HUVECs. Sodium Salicylate inhibited activation of NF-κB by preventing phosphorylation and subsequent degradation of the inhibitor IκB-α. Salicylate did not have an effect on tumor necrosis factor-α (TNF-α) induced phosphorylation of the transcription factor ATF-2. Sodium Salicylate inhibited the TNF-α-induced increase in mRNA concentrations of adhesion molecules and statistically significantly inhibited TNF-α induced surface expression of the adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) at concentrations above 5 mM and intercellular adhesion molecule-1 (ICAM-1) at concentrations above 10 mM. Sodium Salicylate inhibited neutrophil transmigration without affecting neutrophil adhesion.

Pretreatment of normal human diploid FS-4 fibroblasts with 20 mM Sodium Salicylate inhibited a TNF-mediated increase in tyrosine

phosphorylation of p42/p44 mitogen-activated protein kinase (MAPK); significance of the inhibition increased with length of pretreatment (Schwenger et al., 1996). Inhibition was correlated with an inhibition of the TNF-induced p42 MAPK mobility shift. The effect of Sodium Salicylate was specific for TNF; Sodium Salicylate did not block p42/p44 MAPK tyrosine phosphorylation in response to epidermal growth factor (EGF) stimulation or in response to platelet-derived growth factor. Inhibition was not due to toxicity.

Schwenger et al. (1997) found that 20 mM Sodium Salicylate also inhibited TNF-induced activation of the c-Jun N-terminal kinase (JNK)/ stress-activated protein kinase in normal human diploid FS-4 fibroblasts. It was much less effective in reducing EGF- or interleukin-1 (IL-1)-induced JNK activity. Sodium Salicylate inhibited c-*fos* mRNA induction by TNF. Tyrosine phosphorylation was enhanced by treatment with Sodium Salicylate, and Sodium Salicylate increased p38 kinase activity in COS cells.

The inhibitory effect of Sodium Salicylate on UVB-induced AP-1 activity was evaluated by incubating JB6 cells with Sodium Salicylate at concentrations ranging from 0-4 mM (Huang et al., 1997). The cells were incubated for 30 min and then sequentially exposed to 2 kJ/m^2 UVB. Sodium Salicylate inhibited UVB-induced AP-1 activity at concentrations above 0.25 mM, with complete inhibition at 2 and 4 mM. Sodium Salicylate was not cytotoxic to JB6 cells at these concentrations. Sodium Salicylate did not inhibit AP-1 activity when given after irradiation.

PHARMACOLOGIC EFFECTS

Salicylic Acid

In a study of the interaction of Salicylic Acid and pyridyl-3-methanol in producing anti-inflammatory and teratogenic effects, Cekanova et al. (1974) also reported the effects of Salicylic Acid on lysosomal membrane stability in male and female Sprague-Dawley rats. β-Glucuronidase and acid phosphatase were used as marker enzymes. Salicylic Acid at a concentration of 1 mM increased lysosomal membrane stability, but concentrations of 10^{-1} and 10^{-2} mM did not.

The effect of topical application of an ointment containing 3% Salicylic Acid and 0.05% betamethasone dipropionate on plasma cortisol concentrations was evaluated using two male and three female subjects with extensive psoriasis and two male and one female subject with extensive eczema (Gip and Hamfelt, 1976). The ointment was applied twice daily for 2 wks. The treated area ranged from 8-18 dm^2, and the amount of ointment applied per day ranged from 10-15 g. Blood samples were taken twice a week prior to and during dosing. No effect on adrenal gland function, as determined by monitoring plasma cortisol concentrations, was observed. Salicylate was not detected in the plasma.

The effect of Salicylic Acid on isolated rat hepatocytes was determined (Walker et al., 1989). Incubation with Salicylic Acid resulted in a dose-dependent decrease in alanine aminotransferase activity in the medium. A small increase in aspartate aminotransferase was also observed with 1.0 and 2.0 mg/ml salicylate.

Sodium Salicylate

Female albino rats were dosed i.p. with 100 mg/ml Sodium Salicylate in sodium chloride, pH 7.0, to determine the hepatic effects (Bullock et al., 1970). Control animals were given sodium chloride only. Sodium Salicylate had no effect on total hepatic ATP content, but Sodium Salicylate altered the distribution between the mitochondrial and supernatant fractions, increasing the proportion of ATP in the supernatant fraction. No changes in hepatic urate oxidase or catalase activities were observed, as were no changes in β-glucuronidase, acid phosphatase, or alanine aminotransferase (ALT). A very small change in the spectrum of cytochrome P_{450} was seen after the addition of 5 mM Sodium Salicylate to a microsomal suspension *in vitro*. The bile flow rate was "markedly increased" by Sodium Salicylate. Using light microscopy, no gross changes in the liver sections were observed. With electron microscopy, "large numbers" of peroxisomes were observed, and large numbers of multivesicular bodies near the Golgi apparatus were noted.

Dawkins et al. (1970) demonstrated that Sodium Salicylate can displace long-chain fatty acids from human plasma proteins and bovine albumin *in vitro*.

The effect of Sodium Salicylate on blood pH was determined in four studies using Sprague-Dawley rats (Hill, 1971). In the first study, 200 mg/kg

Sodium Salicylate (expressed as Salicylic Acid) was infused into groups of five to eight anesthetized animals. After 1 h, the animals were treated with a 10% sodium bicarbonate infusion, saline (controls), or inhalation of a 20:80 carbon dioxide: oxygen mixture. The animals were killed after 30 min, and blood pH and plasma and tissue salicylate concentrations were determined. The study was repeated using rats with ligated kidneys.

In the rats with the intact kidneys, the blood pH range from 7.69-7.93, 7.45-7.58, and 6.68-6.93 after treatment with sodium bicarbonate, saline, and carbon dioxide, respectively. In the animals with ligated kidneys, the ranges were 7.68-7.90, 6.46-7.53, and 6.75-6.94, respectively. Following treatment with sodium bicarbonate, saline, and carbon dioxide, the muscle/plasma salicylate ratios were 0.4 and 0.36, 0.38 and 0.47, and 0.58 and 0.56 for animals with intact and ligated kidneys, respectively; the brain/plasma salicylate ratios were 0.27 and 0.23, 0.26 and 0.28, and 0.45 and 0.45 for animals with intact and ligated kidneys, respectively; and the liver/plasma ratios were 0.55 and 0.55, 0.55 and 0.72, and 0.93 and 0.98 for animals with intact and ligated kidneys, respectively.

In the second study, three rats were dosed by i.p. injection with 400 mg/kg Sodium Salicylate. The animals were killed 3 h after dosing, and arterial blood pH and plasma and tissue salicylate concentrations were determined. The blood pH ranged from 7.40-7.51. The amount of salicylate found in the plasma, muscle, brain, and liver was 425, 174, 141, and 301 µg/g, respectively.

In the third study, six rats were killed with i.p. injections of 1380-1500 mg/kg Sodium Salicylate. Tissues were taken a few minutes after the animals died. Survival time was 20-34 min. The amount of salicylate found in the muscle, liver and brain was 928, 1329, and 433 µg/g, respectively.

In the fourth study, two groups of three anesthetized rats were infused i.v. with 400 mg/kg Sodium Salicylate. After 30 min, the animals were given 0.1 ml/min infusions of 10% sodium bicarbonate or 0.9% sodium chloride. The animals were killed after 1 h and arterial blood pH and plasma and tissue salicylate concentrations were determined. In the animals given saline, the blood pH ranged from 7.47-7.50, and the amount of salicylate found in the plasma, muscle, brain, and liver was 570, 234, 181, and 367 µg/g, respectively. In the animals given sodium bicarbonate, the blood pH range from 7.79-7.85 and the amount of salicylate found in the plasma, muscle, brain, and liver was 459, 159, 109, and 214 µg/g, respectively.

The protective effects of Sodium Salicylate against the gastric necrosis produced by ethanol and HCl, and against aspirin induced ulcers, was studied in Sprague-Dawley rats (Robert, 1981). Oral doses of 5-50 mg/kg and s.c., doses of 150 and 300 mg/kg were used. Sodium Salicylate was dose-dependently protective against gastric necrosis. The concentration at which aspirin induced ulcers were reduced by 50% was 40 mg/kg orally and 100 mg/kg s.c.

ANIMAL TOXICOLOGY

ACUTE DERMAL TOXICITY

Salicylic Acid

An occlusive patch containing 2 g/kg Salicylic Acid was applied to the clipped skin of five male and five female rats for 24 h (Bomhard, 1989). The animals were observed for 14 days. None of the animals died. One h after dosing, "poor general condition and piloerection" were observed; all animals were normal by day 2. At day 14 necropsy, "slightly swollen" livers were observed in two female animals. The dermal LD_{50} of Salicylic Acid was > 2 g/kg for rats.

Butyloctyl Salicylate

Five male and five female Sprague-Dawley rats were used to determine the dermal LD_{50} of Butyloctyl Salicylate (Huntingdon Life Sciences, 1998b). The hair was clipped from the back of each animal, and 2 g/kg Butyloctyl Salicylate was applied under an occlusive patch for 24 h. All animals surivived until study termination. Six animals had "slight red stains on the snout" on the day of dosing. The dermal LD_{50} of Butyloctyl Salicylate was >2 g/kg for rats.

Ethylhexyl Salicylate

The acute dermal LD_{50} of Ethylhexyl (Octyl) Salicylate was >5 g/kg for rabbits (Anonymous, 1976).

Methyl Salicylate

The acute dermal LD_{50} of Methyl Salicylate was >5 g/kg for rabbits (Opdyke, 1978).

In a limit test performed using rats following OECD Test Guideline No. 402, the acute dermal LD_{50} of Ethylhexyl (Octyl) Salicylate was >2 g/kg (Haarmann and Reimer, 1991).

Tridecyl Salicylate

Five male and five female CD rats, housed five per cage, were used to determine the acute dermal toxicity of Tridecyl Salicylate in a limit test (Biolab, 1998a). Two g/kg of the test material was applied undiluted for 24 h to a shaved area under an occlusive patch. The animals were observed for 14 days. None of the animals died. Body weights were normal, and no signs of toxicity were observed. The dermal LD_{50} of Tridecyl Salicylate was >2.0 g/kg for rats.

ACUTE ORAL TOXICITY

Salicylic Acid

Groups of five cats were dosed with Salicylic Acid (Bekemeier, 1955). One animal given 1.0 g/kg and three given 0.35-0.45 g/kg died. All animals given 0.1-0.18 g/kg Salicylic Acid survived.

Sado (1973) examined the synergistic effect on the oral toxicity of Salicylic Acid in olive oil and 2% and pure furylfuramide using dd mice. Mixtures made either with equal quantities or according to LD_{50} ratios were not synergistic.

The oral LD_{50} of Salicylic Acid was 891 mg/kg for rats (Sax, 1979) and 480 mg/kg for white mice (Prokopovich, 1963).

A group of four to six rats was dosed orally with 0.5 ml of 100 mg/ml Salicylic Acid in PEG 400 (Strom and Jun, 1974). The animals were killed 1 h after dosing, and their stomachs were removed. A "large amount of bleeding" and gastric lesions were observed.

The oral LD_{50} of Salicylic Acid was determinec using groups of 10 fasted Wistar rats (Hasegawa et al., 1989). The oral LD_{50} of aq. Salicylic Acid in gum arabic was 1580 and 1250 mg/kg for male and female rats, respectively.

Groups of four male albino Wistar rats were given a single oral dose of 800 mg/kg Salicylic Acid in distilled water, pH 7.2 (Walker et al., 1989). Hepatic and plasma parameters were determined after 4 h. Compared to controls, a significant increase in liver-to-body weight ratios and plasma ALT and a significant decrease in glutathione was observed.

Groups of 10 male Fischer 344 rats, 3 and 12 mos old, were given orally 5 ml/kg of 500 mg/kg Salicylic Acid in corn oil/DMSO (5:1) (McMahon et al., 1991). Control animals were given vehicle or were untreated. Urine samples were collected at various intervals up to 72 h after dosing, at which time the animals were killed. Two of the 3 mos old test animals were killed at 16 h due to moribund appearance, and two of the 12 mos old animals died between 16-24 h; the cause of death was not determined.

Urine output was significantly increased in both test groups from 8-72 h; the increase was significantly greater in the 12 mos animals compared to the 3 mos animals. Glucose and protein excretion were significantly increased in both groups at 8-24 h and 4-48 h, respectively; at 24 h, urinary glucose was significantly greater for the 12 mos animals. In examining the effect on proximal tubular enzyme excretion, Salicylic Acid significantly increased excretion of *N*-acetyl-β-glucosaminidase (NAG) at 4-72 h, alkaline phosphatase (AP) at 4 and 16 h in both test groups and at 8 h in 3 mos animals, and ALT in 3 mos rats at 4 and 8 h and in 12 mos rats at 24-72 h. Compared to 3 mos animals, NAG was greater at 4, 24, and 48 h, AP was greater at 24-72 h, and ALT was greater at 24 h in 12 mos animals. In examining the effect on distal tubule enzyme excretion, AST was significantly increased from 8-72 h and urinary lactate dehydrogenase (LDH) was increased at 4-48 h. Compared to 3 mos animals, AST and LDH were significantly greater in 12 mos animals at 24 h. Microscopic evaluation showed proximal tubular regeneration in the renal cortex of 3 and 12 mos animals at 72 h. Affected tubules were single or in small clusters occurring throughout the cortex, and the epithelium had hyperplasia, anisocytosis, anisokaryosis, and cytoplasmic hyperchromia. The lumens of many of the tubules contained eosinophilic stained granular material that was consistent with necrotic cellular debris.

Butyloctyl Salicylate

The acute oral toxicity of Butyloctyl Salicylate was determined according to the methods described in the Federal Hazardous Substances Act (FHSA) (Leberco•Celsis Testing, 1996a). The animals were dosed orally with 5 g/kg Butyloctyl Salicylate and observed for 14 days. All animals surivived until study termination. All animals had "yellow anogenital staining" on the days 1 and 2, and it was present for one female animals on day 3. The oral LD_{50} of Butyloctyl Salicylate was >5 g/kg.

Ethylhexyl Salicylate

The acute oral LD_{50} of Ethylhexyl (Octyl) Salicylate was > 5 g/kg for rats (Anonymous, 1976).

In a limit test performed using rats following OECD Test Guideline No. 401, the acute oral LD_{50} of Ethylhexyl (Octyl) Salicylate was >2 g/kg (Haarmann and Reimer, 1991).

Isodecyl Salicylate

A group of 10 male Wistar albino rats was used to determine the acute oral toxicity of Isodecyl Salicylate (Vevy Europe, 1973a). A single oral dose of 5.0 ml/kg (4830 mg/kg) was given at a concentration of 50% in peanut oil. The test volume was 0.01 ml/g. None of the animals died. "Symptoms of central nervous system depression lasting 2 days after treatment" were observed. The researchers concluded that Isodecyl Salicylate did not "produce significant acute systemic effects."

Methyl Salicylate

Rats were given an oral dose of 1-3 g/kg Methyl Salicylate in a 20% suspension in a gum syrup mixture (Giroux et al., 1954). The LD_{50} was approximately 1.25 g/kg.

The oral LD_{50} of Methyl Salicylate in 2% methylcellulose (equiv. to 100 mg/kg Salicylic Acid) was 1110, 1250, and 1300 mg/kg for mice, rats, and rabbits, respectively (Davison et al., 1961).

The oral LD_{50} of Methyl Salicylate was 887 mg/kg for rats and 1060 mg/kg for guinea pigs (Jenner et al., 1964). Groups of 10 fasted animals were used. After dosing, "depression" was observed in rats. In guinea pigs, convulsions were observed and Methyl Salicylate irritated the gastrointestinal tract. The rats died in 4-18 h and the guinea pigs died in 1 h - 3 days.

Four conscious (three males and one female) and three anesthetized (two males and one female) dogs were used to examine the toxicity of Methyl Salicylate (Lacroix and Ferragne, 1964). In the conscious animals, one was dosed via gastric catheter with 1.7 g/kg and three (one per dose) were given intraduodenally 0.6, 1.8, or 4.7 g/kg Methyl Salicylate. Vomiting and changes in respiration were noted in all animals. The female animal dosed with 1.8 g/kg and a male animal dosed with 4.7 g/kg died. In the anesthetized animals, 0.6, 3.1, or 5 g/kg Methyl Salicylate were administered gastrically. An increase in respiratory amplitude was observed in all animals.

Mongrel dogs were given an intragastric dose of 700 mg/kg Methyl Salicylate, and blood samples were taken over a 4-5 h period (Ojiambo, 1971a; 1971b; 1971c; 1972; 1975; Ojiambo et al., 1972). Arterial plasma salicylate concentrations and plasma flow increased for 4 h after dosing, peaking at 41.3 mg% and 9.6 ml/min/100 ml, respectively. An increase in creatine phosphokinase activity was observed in the coronary effluent and muscle bed of the hind limb, indicating myocardial cell damage. Total body oxygen consumption rose steadily and peaked at 4 h, with a two-fold increase over baseline values. Respiratory alkalosis was initially observed, and metabolic acidosis was seen after 3 h. Arterial potassium and lactate concentrations increased. A slight increase in PO_2 was reported. A net efflux of orthophosphate was observed after 2 h. A swelling of cardiac muscle cells, with separation of myofibrils and "bulging" of sarcolemma, was observed. A dilation of sarcoplasmic reticulum and abnormalities in the mitochondria were noted.

A group of four to six rats was dosed orally with 0.5 ml of Methyl Salicylate (Strom and Jun, 1974). The animals were killed 1 h after dosing, and their stomachs were removed. Some slight redness and irritation of the stomach mucosa, but no bleeding or ulceration, was observed.

The oral LD_{50} was reported by Opdyke (1978) to be 700 mg/kg for guinea pigs and 2800 mg/kg for rabbits; it was noted that administration of 0.5 ml Methyl Salicylate by gavage caused slight redness and irritation of the gastric mucosa. Sax (1979) reported that the oral LD_{50} of Methyl Salicylate was 2100 mg/kg for dogs.

Based on the results of a short-term study (described later), the calculated oral LD_{50} of Methyl Salicylate was 1440 mg/kg for CD-1 mice (Research Triangle Institute, 1984).

The oral LD_{50} of Methyl Salicylate was reported to be 2800, 700, 1220, 1060, and 580 mg/kg for rabbits, guinea pigs, male rats, female rats, and mice, respectively (Rumyantsev et al., 1992).

Sodium Salicylate

The oral LD_{50}s of Sodium Salicylate for the mouse, rat, and rabbit were 0.9, 1.6, and 1.7 g/kg, respectively (Hart, 1947).

The oral LD_{50} of Sodium Salicylate in 2% methylcellulose (equiv. to 100 mg/kg Salicylic Acid) was 1070 mg/kg for mice (Davison et al., 1961).

Six male albino rats were given a single oral dose of 300 mg/kg Sodium Salicylate, pH 6.1, and killed 1 h after administration (Wooles et al., 1967). A negative control group of five rats was given saline. Plasma free fatty acids were reduced 46% below control values, and plasma triglyceride concentrations were reduced 60%. The liver weights of treated animals were slightly but significantly decreased in test animals compared to controls. Hepatic triglyceride concentrations were similar to control values.

Using groups of eight to 10 male Fischer 344 rats, the oral LD_{50} of Sodium Salicylate was 1126 mg/kg (Pryor et al., 1983).

The oral LD_{50} of Sodium Salicylate was determined using groups of 10 fasted Wistar rats (Hasegawa et al., 1989). The oral LD_{50} of aq. Sodium Salicylate was 1050 and 930 mg/kg for male and female rats, respectively.

Tridecyl Salicylate

The acute oral toxicity of Tridecyl Salicylate was determined using 10 male albino Swiss mice (Vevy Europe, 1973b). The animals were dosed by gavage with 5 ml /kg (4830 mg/kg) Tridecyl Salicylate in peanut oil at a concentration of 50%. The dose volume was 0.01 ml/g. The LD_{50} was >2.05 ml/kg.

ACUTE INHALATION TOXICITY

Methyl Salicylate

Methyl Salicylate, heated to 80°C and given by inhalation for an unknown duration to white mice and rats was not lethal; the LC_{50} was >400 mg/m^3 (Rumyantsev et al., 1992).

In an acute inhalation study, again of unknown exposure duration, white rats were exposed to 18, 69, and 114 mg/m^3 Methyl Salicylate (Rumyantsev et al., 1992). The high exposure level caused a decrease in summation threshold indicator (STI), research activity (RA), and orientation reaction (OR) (nervous system functions) and in lactate dehydogenase acivity in the serum, an increase in alanine aminotransferase activity, and a decrease in the time to start of blood coagulation. Exposures of 18 and 69 mg/m^3 reportedly led to an unspecified change in the indicators of nervous system functioning.

ACUTE PARENTERAL TOXICITY

Salicylic Acid

Sax (1979) reported that the subcutaneous LD_{50} of Salicylic Acid was 520 mg/kg for mice.

Ethylhexyl Salicylate

The lowest lethal i.p. dose of Ethylhexyl (Octyl) Salicylate for mice was 200 mg/kg (Anonymous, 1976).

Isodecyl Salicylate

The acute i.p. toxicity of Isodecyl Salicylate was determined using a total of 40 male Wistar albino rats (Vevy Europe, 1974b). The animals were given a single dose of 0.62, 1.25, 2.5, or 5.0 ml/kg (604, 1208, 2415, or 4830 mg/kg, respectively) with concentrations of 6.25, 12.5, 25, and 50% (v/v) in peanut oil. None of the animals in the 0.62 ml/kg group died within 14 days of dosing. One, four, and 10 animals in the 1.25, 2.5, and 5.0 ml/kg groups, respectively, died 2-7 days after dosing. "Symptoms of central nervous system depression lasting 2 days after treatment" were reported. The acute i.p. LD_{50} in rats was 2.5 ml/kg.

Methyl Salicylate

The minimum lethal dose was 1.5 g/kg in guinea pigs, and the lethal s.c. doses were 2.7-2.75, 4.25-4.35, and 2.25 g/kg for guinea pigs, rabbits, and dogs, respectively (Opdyke, 1978).

Rats and guinea pigs were dosed with 0.5, 0.75, or 1 g/kg Methyl Salicylate in an alcohol suspension (Giroux et al., 1954). The LD_{50} for rats and guinea pigs ranged from 0.75-1 g/kg.

Sodium Salicylate

One male mongrel dog was dosed i.v. with 0.3 and one with 0.6 g/kg Sodium Salicylate (Rapoport and Guest, 1945). The animal dosed with 0.3 g/kg had moderate hyperventilation at 5 h. The increase in blood pH and decrease in CO_2 tension was greatest at 1.5 h after dosing. The animal dosed with 0.6 g/kg was "breathing very deeply" within 20 min of dosing and died 3.5 h after dosing. A blood sample taken 45 min after dosing had an elevated pH, slight decreased CO_2 content, and a markedly decreased CO_2 tension. The values were more normal at 3 h.

Groups of female A/Jax mice were given a single i.m. dose of 12-18 mg Sodium Salicylate/20 g body wt in 0.1 ml distilled water to determine the LD_{50} (Eriksson, 1970). The i.m. LD_{50} for A/Jax mice was 15.2 mg /20 g body wt.

The i.p. LD_{50} doses for adult and 5-day-old Holtzman rats were 780 and 512 mg/kg, respectively (Goldenthal, 1971).

Groups of 30-50 gravid and non-gravid Konárovice mice were used to determine the i.p. LD_{50} of Sodium Salicylate (Nezádalová et al., 1973). The gravid animals were dosed on days 7, 14, or 20 of gestation or days 7 or 14 after parturition. The LD_{50} values were 760 mg/kg for control animals, 760, 535+, and 520+ mg/kg for animals dosed on days 7, 14, and 20 of gestation, respectively, and 700 and 780 mg/kg for animals dosed on days 7 and 14 after parturition, respectively. The toxicity of Sodium Salicylate was increased in gravid mice.

Sax (1979) reported that the i.v. LD_{50} for mice was 780 mg/kg.

Male Sprague-Dawley rats, 3 and 12 mos old, were given a single i.p. injection of 500 mg/kg Sodium ^{14}C-Salicylate (250 mCi/mmol) in saline (Kyle and Kocsis, 1985). A control group was dosed with saline. The animals, which were placed in metabolism cages, were killed 1.5, 3, 6, 12, or 24 h after dosing; both kidneys were removed.

No changes were observed in control animals. In 3 mos old animals, dilation and vacuolization of proximal tubule cells occurred 6 h after dosing, and cytoplasmic eosinophilia was also observed. At 12 h, the kidneys were normal. In the 12 mos old animals, focal areas of proximal tubular necrosis and interstitial edema, characterized by extensive nuclear pyknosis and karyolysis and degeneration of the luminal membrane, were observed at 6 and 24 h. Regeneration of the tubular epithelium was observed at 24 h. Blood urea nitrogen (BUN) concentrations were significantly elevated in 3 mos old animals at 3 and 6 h; the values were normal at 12 h.

A more severe change (compared to younger animals) in BUN that was significantly different from control animals was observed in 12 mos old animals at 3, 6, 12, and 24 h. In 3 mos old animals, a significant increase in urinary protein was found at all time intervals, and small to moderate amounts of blood were found in the urine. In 12 mos old animals, a greater increase in urinary protein and blood was observed. Significant glucosuria was observed in 12 mos old animals at each time interval. Glucose was not detected in the urine of 3 mos old animals. No difference in excreted radioactivity was observed between the 3 mos and 12 mos old animals. In examining urinary metabolites, excretion of SUA and gentisuric acid was decreased 71 and 80%, respectively, in the older animals. Maximal covalent binding to mitochondrial protein occurred after 3 h in both groups. Mitrochondrial binding declined in 3 mos old animals but was steady in 12 mos old animals.

Tridecyl Salicylate

The acute i.p. toxicity of Tridecyl Salicylate was determined using 30 male Swiss albino mice (Vevy Europe, 1973c). The animals were dosed with 1.25, 2.5, or 5.0 ml/kg (1208, 2415, 4830 mg//kg) Tridecyl Salicylate at a concentration of 12.5, 25, or 50% in peanut oil. The dose volume was 0.01 ml/g. Tridecyl Salicylate had a LD_{50} of >1.5 ml/kg.

SHORT-TERM ORAL TOXICITY

Salicylic Acid

Groups of four male albino Wistar rats were dosed orally for 3 days with 500 mg/kg/day Salicylic Acid in distilled water, pH 7.2 (Walker et al., 1989). Hepatic and plasma parameters were determined 18 h after the last dose. Compared to controls, a significant increase in aniline hydroxylase, glutathione, plasma aspartate aminotransferase (AST), and plasma ALT activities and a significant decrease in glucose-6-phosphatase activity was observed.

Butyloctyl Salicylate

Groups of five male and five female Sprague-Dawley CD rats were dosed orally with 15, 150, or 1000 mg/kg in corn oil daily for 28 days, while a control group was given vehicle only (Huntingdon Life Sciences, 1998c). The animals were observed for signs of toxicity, and body weights and feed consumption were determined periodically. Neurobehavioral studies were performed prior to and at the termination of dosing. Hematology and clinical chemistry evaluations were performed at study termination. The animals were killed at study termination. The tissues of animals of the 1000 mg/kg and control groups were examined microscopically.

Excessive salivation was observed in one female of the high dose group during wk 2 and in two males and two females of the high dose group during wk 3; one of the females also had "slight red stains on the snout" during wk 3. Another female of the high dose group had lacrimation during wk 3. Mean prothrombin and activated partial thromboplastin times were increased in animals of the high dose group. Body weights, feed consumption, motor activity, functional observational batteries, organ weights, and microscopic examinations were similar for all animals. The no-observable effect level (NOEL) was 150 mg/kg/day.

Methyl Salicylate

Groups of two dogs, one male and one female, were given 50-1200 mg/kg synthetic Methyl Salicylate (99% pure) orally in capsule form daily 6 days per wk for up to 59 days (Webb and Hansen, 1963). Clinical observations were recorded during the study. All animals dosed with ≥500 mg/kg Methyl Salicylate had weight loss and died or were killed due to moribund condition within 1 mo of study initiation. One animal given 800 mg/kg and both given 1200 mg/kg Methyl Salicylate vomited for 3-4 h following each administration. Microscopically, moderate to marked fatty changes were observed in the liver of one animal given 800 mg/kg and both given 1200 mg/kg. Animals given 500 mg/kg had diarrhea and weakness during the last 3-4 days prior to death. No adverse effects were seen in animals given 50-250 mg/kg Methyl Salicylate.

In a study to determine the effect of Methyl Salicylate on bone, groups of 10 male rats were fed a diet containing 20,000 ppm Methyl Salicylate for 1, 2, 3, 4, or 5 days (LaWall and Harrisson, 1964). Two animals per group were killed on days 2, 4, 6, 8, and 10 after discontinuation of the test diet. No bone lesions were observed.

Groups of 12 male and 12 female rats were fed a diet containing 6000, 9000, or 12,000 ppm Methyl Salicylate for 7 wks, while a control group was fed untreated feed (LaWall and Harrisson, 1964). X-rays were taken and two males and two females per group were killed weekly as of wk 2. Bone lesions were observed for animals of the 12,000 ppm dose group, but they were not seen in the other dose groups. Mean body weights and feed consumption correlated inversely with dose. Serum salicylate concentrations correlated with dose.

Groups of 10 male and 10 female Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.6, 0.9, 1.2, or 2.0% Methyl Salicylate for 11 wks (Abbott and Harrisson, no date; LaWall and Harrisson, 1964). X-rays were taken of two animals per group weekly; the animals were killed 1 wk after x-ray and the femurs of some animals were examined microscopically. Mean body weights were decreased in the 2.0% group after wk 7. Positive bone lesions were seen at wk 2 in animals of the 2.0% group, and unequivocal changes were seen at wk 5 in the 1.2% group. Microscopic changes were seen at wks 2 and 8 in these groups, respectively. No changes were seen in the other test groups.

Groups of five male rats were fed 20,000 ppm Methyl Salicylate and a "protein diet" (consisting of 75% basic feed and 25% casein) for 7 wks, with one group given water and one given 40% dextrose; a control group was fed the protein diet only (LaWall and Harrisson, 1964). Mean body

weights were decreased in the test group given water. The animals in the test group given dextrose consumed less feed, reducing the Methyl Salicylate intake to 60-80% of that consumed by the group given water. An increase in calcellous bone was seen in the group given Methyl Salicylate with water.

Groups of 10 male and 10 female rats were fed 12,000 or 20,000 ppm Methyl Salicylate or 12,000 ppm Methyl Salicylate and given i.p. 1 unit/day parathyroid extract and groups of five male and five female rats were fed 12,000 ppm Methyl Salicylate alone or with 1290 ppm $CaSO_4 \cdot 2H_2O$, 10 mg/day Ca^{++} i.p., cod liver oil (equal to 100 units vitamin D/100 g feed), or 1000 mg/day vitamin C i.p.; the animals were dosed for 8 wks (LaWall and Harrisson, 1964). Bone lesions were seen in all animals dosed with Methyl Salicylate only. Body weights were decreased in most test groups. No bone lesions were seen in the animals given parathyroid hormone, $CaSO_4 \cdot 2H_2O$, Ca^{++}, cod liver oil, or vitamin C.

In an 11 wk study, groups of five male and five female rats were fed 12,000 ppm Methyl Salicylate, alone, with 250, 750, or 1250 ppm calcium carbonate in feed, or with 45 mg/day Ca^{++} given i.p. (LaWall and Harrisson, 1964). In the Methyl Salicylate only group, bone lesions were seen at 4 wks (the earliest time x-rays were taken). In the calcium carbonate groups, no bone lesions were observed; at wk 11, survival was 50, 60, and 60% in the 250, 750, and 1250 ppm calcium carbonate groups, respectively. In the Ca^{++} group, the animals were killed because calciphylactic lesions occurred at the site of injection.

Group of eight male and eight female CD-1 mice were dosed orally with 50, 100, 250, 500, or 1000 mg/kg Methyl Salicylate in corn oil for 14 days (Research Triangle Institute, 1984). A control group was given vehicle only. Two females, one female and one male, and two females and three males of the 50, 100, and 1000 mg/kg groups, respectively, died during the study. Piloerection and dehydration were observed for these animals. The mortality rate was significantly increased in the 1000 mg/kg group compared to the other groups.

A study following the same protocol and using the same doses was performed by Environmental Health and Research Testing, Inc, (1984). In this study, one control and two 1000 mg/kg animals died due to pulmonary congestion or cardiac myodegeneration and tubular nephrosis.

Sodium Salicylate

Rats were given 400-600 mg/kg of 10% aq. Sodium Salicylate for 4-21 days, and the effects on the liver and kidneys were examined (Barbour and Fisk, 1933). The following were observed in the liver: no change (1 animal, 400 mg/kg - 4 doses; 1 animal, 400 mg/kg - 7 doses); marked congestion and vacuolization (1 animal, 400 mg/kg - 4 doses; 1 animal, 400 mg/kg - 7 doses); slight to moderate focal necrosis with moderate vacuolization (3 animals, 400 mg/kg - 14 doses); marked necrosis and vacuolization (1 animal, 400 mg/kg - 21 doses); moderate necrosis and vacuolization (3 animals, 400 mg/kg - 21 doses; 4 animals, 500 mg/kg - 21 doses); slight necrosis and vacuolization (1 animal, 400 mg/kg - 21 doses); widespread necrosis and vacuolization (1 animal, 500 mg/kg - 7 doses); and marked vacuolization with moderate focal necrosis (5 animals, 600 mg/kg - 7 doses; 1 animal, 600 mg/kg - 11 doses).

The following were observed in the kidneys: no change (1 animal, 400 mg/kg - 7 doses); moderate necrosis and degeneration of the tubular cells (2 animals, 400 mg/kg - 4 doses); marked necrosis and degeneration of tubular cells (1 animal, 400 mg/kg - 7 doses); slight necrosis of tubular cells (3 animals, 400 mg/kg - 14 doses; 1 animal, 400 mg/kg - 21 doses); marked necrosis of tubular cells (3 animals, 400 mg/kg - 14 doses; 1 animal, 600 mg/kg - 11 doses); moderate necrosis of tubular cells (3 animals, 400 mg/kg - 21 doses); moderate necrosis and degeneration of convoluted tubules (1 animal, 500 mg/kg - 7 doses; 4 animals, 500 mg/kg - 21 doses); and slight to moderate necrosis and degeneration of tubular cells (5 animals, 600 mg/kg - 7 doses). The animals of the 600 mg/kg group died within 10 days. Half of the animals of the 500 mg/kg dose group died within 2 wks.

Four dogs were given 300 mg/kg of 10% aq. Sodium Salicylate for 2 wks, and the effect on liver function was examined on alternate days using the Rosenthal bromsulphalein dye excretion test (Barbour and Fisk, 1933). No gastric or duodenal ulcers were seen. There was no marked dye retention. At microscopic examination, widespread vacuolization with moderate degrees of necrosis was seen in the

centers of the lobules of the liver and widespread necrosis and degeneration of the tubules were seen in the kidneys. Only the glomeruli of the kidneys were intact.

A group of six male and six female rats was fed a diet containing 21,020 ppm Sodium Salicylate for 11 wks (LaWall & Harrisson, 1964). Sodium Salicylate was introduced at 50% of the dose during wks 1-2 and at 75% of the dose during wks 3-4. A negative control group of three males and 12 females was fed the basal diet. In the test animals, weight gain was inhibited and feed consumption was reduced compared to controls. A positive increase in cancellous bone was observed in the test animals. Mortality was significant as of wk 3 and approached 100% by wk 7.

A group of six male albino rats was dosed orally with 300 mg/kg Sodium Salicylate, pH 6.1, for 7 days and killed 1 h after the last dose (Wooles et al., 1967). A control group of five rats was given saline. No change in the plasma free fatty acids was observed, and hepatic and plasma triglyceride concentrations were similar for treated and control animals.

Wooles et al. (1967) also examined the effect of feeding standard chow or chow containing 1% cholesterol and 0.5% cholic acid to groups of 11-16 male albino rats that were dosed orally with 300 mg/kg Sodium Salicylate or given saline only for 7 days. The animals were given the appropriate diet immediately after the initial dose. The animals were fasted for 16 h after the last dose and then killed.

In the test animals fed the basic diet, hepatic triglyceride concentrations were not different from controls, while plasma triglyceride concentrations were increased 84%. In the animals fed the high-cholesterol diet, hepatic free and esterified cholesterol values were similar for test and control animals, while plasma total and free cholesterol values were increased 22 and 35%, respectively, in the treated animals as compared to controls. A mean increase in liver weight of 20% was observed in all animals given Sodium Salicylate.

Groups of 10 male Fischer 344 rats were dosed by gavage 5 days/wk for 4 wks with Sodium Salicylate in distilled water (Pryor et al., 1983). The 28-day LD_{50} was 646.5 mg/kg.

SHORT-TERM INHALATION TOXICITY

Methyl Salicylate

The inhalation toxicity of Methyl Salicylate was determined using a group of four female Alderley Park rats (Gage, 1970). The animals were exposed to twenty 7 h exposures at a concentration of 120 ppm in a saturated atmosphere at 700 mg/m^3. No toxicity was observed; and the organs appeared normal at necropsy.

SHORT-TERM PARENTERAL TOXICITY

Methyl Salicylate

Groups of two rats were dosed s.c. with 400, 600, 900, or 1200 mg/kg/day Methyl Salicylate for 2 wks (LaWall and Harrisson, 1964). One animal of the 900 and one of the 1200 mg/kg dose groups died within 48 h; all others survived until the termination of dosing. No bone lesions were observed.

Rats, five males and five females per group, were dosed i.p. with 0.025 mg/day Methyl Salicylate; one group was also fed a diet containing 3000 ppm calcium carbonate (LaWall and Harrisson, 1964). No bone lesions were observed.

Ten male and 10 female rats were dosed i.p. with 0.05, 0.1 (divided), and 0.2 ml/day Methyl Salicylate from wks 0-5, 5-7, and 7-11, respectively, and were fed a diet containing 3300 ppm calcium carbonate (LaWall and Harrisson, 1964). A control group was fed untreated feed. Body weights were similar for treated and control animals. Seven males, eight females, and six males were surviving at wks 5, 7, and 8, respectively. No increase in cancellous bone was seen.

The maximum tolerated dose (MTD) (maximum single dose survived by all animals) of Methyl Salicylate was determined using groups of five A/He mice (Stoner et al., 1973). The animals were given six i.p. injections over a 2-wk period. The MTD was 500 mg/kg Methyl Salicylate.

Sodium Salicylate

A Rhesus monkey was dosed i.v. with 1.1 g/kg Sodium Salicylate in five divided doses over a 30 h period (Rapoport and Guest, 1945). Signs of

toxicity included hyperpnea, flushed face, weakness, and profuse diuresis. The pH of blood drawn 1 h after the last dose was increased to 7.85; CO_2 content was "moderately" decreased and CO_2 tension was "greatly decreased".

A male mongrel dog was dosed i.p. with 1.0 g Sodium Salicylate in divided doses over a 24 h period (Rapoport and Guest, 1945). After the first dose (0.2 g/kg), hyperpnea was extreme and continued until the death of the animal 2 h after the last dose. Diuresis, weakness, and "hyperreflexia" were also observed.

Groups of five male and five female rats were given i.p. doses of 200 mg/kg/day Sodium Salicylate for 8 wks; one group was also given 3000 ppm calcium carbonate in feed (LaWall & Harrisson, 1964). No positive bone effects were observed in animals of either group.

SUBCHRONIC DERMAL TOXICITY

Methyl Salicylate

Groups of three rabbits were dosed dermally with synthetic Methyl Salicylate (99% pure) 5 days per wk for up to 96 days (Webb and Hansen, 1963). A dose of 0.5, 1.0, 2.0, or 4.0 ml/kg was applied to the clipped skin on the back of restrained animals for 6.5 h each day of dosing. The test sites were not wiped because the compound was absorbed. The three animals dosed with 4.0 ml/kg died after 6, 8, and 28 days of dosing; the animals had "anorexia, weight loss, and depression". A "slight sloughing of epidermal scales" was observed for two of the animals dosed with 2.0 ml/kg. No other observations were noted.

All but one animal of the high dose group were examined microscopically. One high dose animal had "several distinct lesions", including dilatation, desquamation, and formation of new atypical epithelium of the renal tubules, a moderate number of small foci of superficial necrosis and sloughing of the skin, foci of moderate necrosis and slight calcification of voluntary muscles, marked vacuolation of pancreatic acinar cells, slight myeloid hyperplasia and shift to the left of bone marrow, and slight hepatitis. These effects were not seen in the other examined high-dose animals, but an effect on the distal portion of the nephrons was indicated. Spontaneous nephritis and mild hepatitis, and slight to very slight dermatitis, was observed in the other animals.

SUBCHRONIC ORAL TOXICITY

Isodecyl Salicylate

Ten male and 10 female Wistar albino rats were fed 0.5% (~500 mg/kg/day) Isodecyl Salicylate in basal diet for 15 wks (Vevy Europe, 1975a). A control group of 10 males and 10 females was given untreated feed. The actual daily dose of Isodecyl Salicylate was 437-531 and 426-505 mg/kg/day for male and female animals, respectively. Body weight gain and feed intake were similar for test and control animals, and no treatment-related observations were reported. Oral administration of ~500 mg/kg/day Isodecyl Salicylate did not produce a significant toxic effect.

Methyl Salicylate

The effect of Methyl Salicylate on bone metabolism and growth was examined using groups of five male and five female Sprague-Dawley rats fed a diet containing 0.2, 0.36, 0.63, 1.13, or 2.0% Methyl Salicylate enriched with 5% hydrogenated fat for 12 wks (Abbott and Harrisson, no date). The animals received 50% of the dose during wks 1-2, 75% of the dose during wks 3-4, and 100% of the dose thereafter. A negative control group was given untreated feed. Males of the 0.63% group and all animals of the 1.13 and 2.0% groups had decreased body weight gains compared to controls. Radiographs taken at wk 10 showed increased density at the metaphyses of the femur, humerus, tibia, and radius of animals of the 1.13 and 2.0% groups.

Groups of five male rats were fed a 5% fat enriched diet containing 0.6 or 2.0% Methyl Salicylate for 12 wks (Abbott and Harrisson, no date). Mortality was 100% in the 2.0% group at wk 6. None of the animals of the 0.6% group died during the study. Bone lesions were observed in the high dose animals.

Five male and five female Sprague-Dawley rats were fed a 5% fat-enriched diet containing 1.2% Methyl Salicylate for 12 wks, while 10 male and 10 female rats were fed the test diet with the addition of 0.3% calcium carbonate (Abbott and Harrisson, no date). Mean body weights were decreased in the Methyl Salicylate group. Mortality was 90 and 15% in the Methyl Salicylate groups

without and with calcium carbonate, respectively. Bone lesions were not observed in the Methyl Salicylate plus calcium carbonate group. In a subsequent study in which 10 male and 10 female rats were fed 2.0% Methyl Salicylate plus 0.33% calcium carbonate for 11 wks, radiographs taken between wks 2-8 did not show any bone lesions (LaWall and Harrisson, 1964). Survival was 70%.

Groups of 20 Osborne-Mendel rats, 10 males and 10 females per group, were given feed containing 0.1 or 1.0% synthetic Methyl Salicylate (99% pure) for 17 wks (Webb and Hansen, 1963). A control group was given basal diet. Body weights were measured weekly. Body weight gains for males and females of the high dose group were significantly decreased compared to controls. No gross or microscopic findings were observed.

A group of 15 Sprague-Dawley rats was fed a diet enriched with 5% fat containing 2.0% Methyl Salicylate for 12 wks; again, it was given as 50% of the dose during wks 1-2 and 75% of the dose during wks 3-4 (LaWall and Harrisson, 1964). A negative control was given untreated feed. Growth and feed consumption were decreased in the Methyl Salicylate group. Survival was 80% at study termination. Bone lesions were observed.

Groups of 10 male Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.6 or 2.0% Methyl Salicylate *ad libitum* or 0.6% Methyl Salicylate in a paired feeding at a ration equal to the mean daily amount of feed consumed by the 2.0% group fed *ad libitum* for 12 wks (LaWall and Harrisson, 1964). Body weights were decreased in the 2.0% *ad libitum* and the 0.6% paired feeding groups. Mortality was 50, 80, and 90% in the 2.0% *ad libitum* group and 60, 70, and 80% in the 0.6% paired feeding group at wks 2, 3, and 4, respectively. Survival was 100% in the 0.6% *ad libitum* group.

In a 12 wk study, groups of 10 male rats were fed a diet containing 4000 ppm or 20,000 ppm Methyl Salicylate and another group was fed a diet containing 20,000 ppm Methyl Salicylate and dosed i.p. with a mixture containing 250 U vitamin A and 25 U vitamin D; the animals of the 20,000 ppm groups were fed a basal diet after 6 wks (LaWall and Harrisson, 1964). Body weights and feed consumption were decreased in both 20,000 ppm test groups during wks 1-6. Bone lesions were observed in both 20,000 ppm groups

Nine male and nine female rats were dosed daily with 12,000 ppm Methyl Salicylate and 1 mg cortisone (injected) for 12 wks (LaWall and Harrisson, 1964). A control group of three males and five females was untreated. Body weights were decreased in the test group, and bone lesions were observed.

In another 12 wk study, groups of 10 male and 10 female rats were fed 12,000 ppm Methyl Salicylate and 3000 ppm calcium carbonate or 1 mg cortisone (injected) and groups of five male and five female rats were fed 12,000 ppm Methyl Salicylate and 100 mg/day vitamin C (injected), a 50-50 water/milk mixture, 2 ml 10% calcium gluconate (i.p.), 12,000 ppm methyl p-OH benzoate, or 4700 calcium citrate (LaWall and Harrisson, 1964).

In the group given calcium carbonate, body weight was not affected and no bone lesions were observed; survival was 85% at 12 wks. In the group given cortisone, body weights were decreased and bone lesions were observed. In the group given vitamin C, the "bone condition was not as severe and constant as usually noted" with 12,000 ppm Methyl Salicylate. No bone lesions were observed with the water-milk mixture, but the intake of dry feed was decreased and the intake of fluid was increased.

The animals of the calcium gluconate group were killed at wk 4 due to the development of calciphylactic lesions at the point of injection; body weights were decreased and bone lesions were not observed. In the animals given methyl p-OH benzoate or calcium citrate, body weights were not affected and bone lesions were not seen.

Sodium Salicylate

A group of six male and six female Sprague-Dawley rats was fed a 5% hydrogenated fat-enriched diet containing 2.1% Sodium Salicylate for 12 wks (Abbott and Harrisson, no date). A control group was given untreated feed. The animals received 50% of the dose during wks 1-2, 75% during wks 3-4, and 100% thereafter. Growth and feed consumption was reduced in the test group. Mortality was 100% at wk 11. Bone lesions were observed in the test group.

The neurotoxic potential of 138-550 mg/kg Sodium Salicylate was determined using groups of nine to 10 male Fischer 344 rats (Pryor et al.,

1983). (The dose concentrations were based on proportions of the short-term LD_{20} [study described previously] .) The animals were dosed 5 days per wk for 15 wks and were tested using a battery of neurobehavioral tests conducted prior to dosing, at 3-wk intervals during dosing, and 3 and 6 wks after the termination of dosing. A control group was dosed with vehicle only.

The LD_{50} during 15 wks of dosing was estimated to be (via linear regression using the short-term LD_{50} value) 366.5 mg/kg. One animal, two animals, and one animal of the 218, 346, and 550 mg/kg dose groups, respectively, died during wks 2-9 of the study; the deaths were not dose-related. Weight gain of test animals was significantly decreased compared to controls as of wk 3 for animals of the 218 and 550 mg/kg dose groups and as of wk 6 for animals of the 346 mg/kg dose group; weight gains were still significantly decreased 6 wks after the termination of dosing. After 15 wks of dosing, the only behavioral change was a dose-related decrease in hindlimb grip strength; this was significant for all groups except the 138 mg/kg dose group. This effect also persisted after 6 wks of recovery.

Groups of five male Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.7 or 2.1% Sodium Salicylate for 12 wks (LaWall and Harrisson, 1964). A negative control group of 10 animals was given basal feed. Mean body weights in the group fed 4000 ppm Sodium Salicylate was decreased compared to controls. Mortality was 100% in the low dose group at wk 7 and in the high dose group at wk 2. Bone lesions were observed with 2.1% Sodium Salicylate.

Tridecyl Salicylate

Ten male and 10 female Wistar albino rats were fed ~500 mg/kg/day Tridecyl Salicylate in basal diet for 15 wks (Vevy Europe, 1975b). A control group of 10 males and 10 females was given untreated feed. No treatment-related observations were seen. Oral administration of ~500 mg/kg/day Tridecyl Salicylate did not produce a significant toxic effect.

SUBCHRONIC INHALATION TOXICITY

Methyl Salicylate

In an inhalation study, male white rats (number per group not specified) were exposed to 1.2, 8, or 40 mg/m^3 Methyl Salicylate for 4 h/day for 4 mos (Rumyantsev et al., 1992). The high dose caused changes in nervous system functioning, a decrease in hemoglobin content and the number of erythrocytes, and a change in serum leucine aminopeptidase and lactate dehydrogenase activity and urinary creatinine content. At microscopic examination, pulmonary focal hemorrhages and hyperplasia were observed in the peribronchial lymphoid tissue and the number of plasmatic cells in the lymphoid follicles was increased. In the kidneys, scaling of the epithelium of the convoluted tubules, focal infiltration, and focal hemorrhages were seen.

CHRONIC ORAL TOXICITY

Methyl Salicylate

Groups of 25 male and 25 female albino rats were fed a diet containing 700 or 2100 ppm (0.07 or 0.21%) Methyl Salicylate for 2 yrs (Packman et al., 1961). A control group was fed basal diet. No adverse effects were reported. Growth, feed consumption, general condition, mortality, and blood and urine chemistries were similar for test and control animals. No gross or microscopic findings were noted.

Groups of 50 littermated Osborne-Mendel rats, 25 males and 25 females, were fed a diet containing 0.1, 0.5, 1.0, or 2.0% Methyl Salicylate for 2 yrs (Webb and Hansen, 1963). (The group fed 2.0% consisted of 24 males and 26 females.) A control group was given basal feed. Weights were measured weekly, and hematological examinations were done on 10 rats per group at 3, 11, 17, and 22 mos. Organs of animals that died were not included in calculations. Tissues from 12, six, and five animals of the control, 1.0%, and 2.0% groups, respectively, were examined microscopically, and 10 leg bones and muscles of an additional 85 rats were examined.

In the high dose group, half of the animals died by wk 8 and all of the animals died by wk 49 of the study. Animals of the 1.0 and 2.0% groups had statistically significant growth inhibition and developed rough hair coats. No hematological effects were observed. Average absolute organ weights were similar for all animals. However, relative organ to body weight ratios for the testes of male animals and for the heart and kidneys of the female animals of the 1.0% groups were significantly increased. Gross lesions of the

pituitary gland were observed in 10 animals of the 0.5% group as compared to four animals in the control group. In the 2.0% group, 29 of the 50 animals had pneumonia.

The authors described the pneumonia as "more acute than that regularly seen". Microscopically, they stated that a "pronounced change" occurred in the bones of animals fed 2.0% Methyl Salicylate. Cancellous bone in the metaphysis was increased as compared to same-age controls; this was observed to a moderate degree in five and a marked degree in four of the nine bones examined from animals of the 2.0% group. Bone lesions were slight in two of 11 and one of 11 bones examined from animals of the 1.0 and 0.5% groups, respectively. The affected bones had fewer osteoclasts, and the number was inversely proportional to the degree of change.

An additional three male and three female Osborne-Mendel rats were fed 2.0% Methyl Salicylate, and the same number was fed basal diet, to assess the bone changes (Webb and Hansen, 1963). Control animals were killed in conjunction with test animal death. One male test animal died on day 11, two males died on day 19, and females died on days 31, 40, and 71. Rough hair coat and growth inhibition was observed for all test animals, with some animals having labored respiration.

Upon gross observation, four of the six animals had slight to moderate pulmonary damage. Focal gastric hemorrhages were present in the glandular portion of three of the test animals. Bone growth was affected. A pathologist reported that "chondroclastic and especially osteoclastic activity [were] virtually completely blocked. Chondroblastic and osteoblastic activity [were] somewhat diminished."

Groups of two male and two female Beagle dogs were given orally in capsule form 50, 150, or 350 mg/kg synthetic Methyl Salicylate (99% pure) 6 days per wk for 2 yrs (Webb and Hansen, 1963). A control group was given a placebo. The animals were weighed weekly, and hematologic evaluations were made at 2 wks, 1, 3, and 6 mos. and 1 and 2 yrs. No compound-related mortality was observed; one animal of the high dose group died from hepatitis on day 33. No hematological effects were observed. Animals of the 150 and 350 mg/kg groups had retarded growth. Enlarged livers were observed in these animals, and the livers had larger hepatic cells than observed in control animals.

In a 30-wk feeding study, groups of five male and five female rats were fed a diet containing 2000, 3550, 6300, 11,250, or 20,000 ppm Methyl Salicylate (LaWall & Harrisson, 1964). During wks 1 and 2, Methyl Salicylate was given at 50% and during wks 3 and 4 it was given at 75% of the final dose. A negative control group was given basal diet. Body weights and feed and water consumption were measured. Mean body weights were significantly decreased for animals of the 11,250 and 20,000 ppm groups; feed consumption was also decreased in these groups. At wk 10, x-rays were taken; animals of the 11,250 and 20,000 ppm dose groups had positive increased bone density in the femur and tibia. This was not seen in the other groups.

The diets of several control and high dose animals were exchanged after 11 wks. The animals that had previously been given control feed and then given Methyl Salicylate lost weight, and the majority died. Those high dose animals switched to control feed started to recover.

Groups of three male and three female beagles were given 150, 300, 500, or 800 mg/kg/day Methyl Salicylate in capsule form for 6.5-7.5 mos; half the dose was administered following the morning and half following the afternoon feeding (LaWall & Harrisson, 1964). A group of two males and four females served as the negative controls. All animals of the 150 and 300 mg/kg test groups and the negative control group and two of the 500 mg/kg test group animals survived until study termination. Four animals of the 500 mg/kg group died between wks 2-8. In the 800 mg/kg group, five animals died during wk 1 and one died during wk 2. Body weights of the animals of the 150 and 300 mg/kg dose groups were similar to control values. One of the two surviving animals of the 500 mg/kg group had "a slight loss in body weight". Hematology and clinical chemistry values were normal for animals of the 150 and 300 mg/kg dose group.

Two animals of the 150 mg/kg and negative control groups and three animals of the 300 mg/kg group were killed after 6.5 mos. The remaining animals of the 150 and 500 mg/kg groups and the negative control group were killed after 7.5 mos. An increase in liver and kidney weights was observed in treated animals. The pathologist reported that 150 and 300 mg/kg Methyl Salicylate did not induce "lesions or other

deleterious alterations".

Groups of four male and four female dogs were given 50 or 100 mg/kg/day and a group of six male and six female dogs was given 167 mg/kg/day Methyl Salicylate in capsule form for 6 mos; half the dose was administered following the morning and half following the afternoon feeding (FDA, 1966). A negative control group of six male and six female dogs was used. All the animals of the low and mid dose group and four males and four females of the high dose and control groups were killed after 6 mos; the remaining high dose and control animals were killed after 8 mos (following a 2 mos non-treatment period).

All animals survived until study termination. During mo 2 of the study, many test animals had dose-related seborrhea oleosum and pyoderma; addition of lard to the diet alleviated this condition. After 6 mos, hematological parameters were normal. At the 6 mos necropsy, one animal from each test group had hyperemic foci of the pyloric mucosa. No test article-related hepatic or renal changes were found, and relative mean liver and kidney weights were within normal range.

DERMAL IRRITATION

Butyloctyl Salicylate

The primary dermal irritation of Butyloctyl Salicylate was determined using rabbits according to FHSA methods (Leberco•Celsis Testing, 1996b). Butyloctyl Salicylate produced very slight to well-defined erythema and edema. One animal had "blanched skin" at the test site and two had flaking skin. The primary irritation index was 2.12. According to the FHSA, Butyloctyl Salicylate was not a primary dermal irritant.

Ethylhexyl Salicylate

Ethylhexyl (Octyl) Salicylate applied undiluted to intact and abraded rabbit skin for 24 h was mildly irritating (Anonymous, 1976).

A primary skin irritation study of undiluted and 1, 5,and 25% solutions of Ethylhexyl (Octyl) Salicylate was performed using groups of six rabbits following OECD Test Guideline No. 404 (Haarmann and Reimer, 1991). The mean scores (24, 48, and 72 h readings) were 0.1, 0.1, 1.7, and 2.5 for erythema and 0.0, 0.0, 0.9, and 1.7 for edema with 1, 5, 25, and 100% Ethylhexyl (Octyl) Salicylate, respectively. No erythema or edema was observed with the ethanol 96%/diethyl-phthalate (DEP) 1:1 w/w vehicle.

Isodecyl Salicylate

The dermal irritation potential of undiluted Isodecyl Salicylate was determined using six male New Zealand white rabbits (Vevy Europe, 1974a). A volume of 0.5 ml containing 500 mg of the test material was applied (believed to be occlusively) for 4 h to both intact and abraded areas, 25 cm^2, on the dorsum of each animal. Four h after application, very slight erythema and/or edema was reported at the abraded sites of four animals. One animal had very slight edema and one had very slight erythema 24 and 48 h after application, respectively, No reaction was observed 7 days after application. The average primary irritation index (PII) was 0.195. The researchers concluded that Isodecyl Salicylate was "not significantly irritant" to the skin of rabbits.

Methyl Salicylate

A modified Draize test was performed to determine the irritation potential of Methyl Salicylate in various vehicles (Yankell, 1972). Methyl Salicylate, 1, 3, or 6%, in a water suspension, PEG 400, 70% ethanol, or 70% ethanol plus emollients was applied under an occlusive patch to the intact skin on the backs of three animals (species not specified). The test sites were scored for irritation at 24 and 72 h.

The irritation index was greatest with 70% ethanol; scores of 1.17, 4.17, and 4.00 were reported with 1, 3, and 6% Methyl Salicylate, respectively. Necrosis was seen in all three animals dosed with 3 and 6% Methyl Salicylate in 70% ethanol. With 70% ethanol plus emollients, scores of 2.17, 3.00, and 3.00 were reported with 1, 3, and 6%, respectively; necrosis and intradermal and s.c. hemorrhage were seen at all doses. The water suspension of 1, 3, and 6% Methyl Salicylate produced irritation indices of 0.0, 0.83, and 1.83, respectively, and with PEG 400, indices of 0.33, 0.50, and 0.50, respectively, were reported.

Although details were not provided, Opdyke (1978) reported that Methyl Salicylate was severely irritating to guinea pig skin and moderately

irritating to intact and abraded rabbit skin when applied under an occlusive patch for 24 h.

Rumyantsev et al. (1992) reported that a single application of Methyl Salicylate to the skin or rabbits and guinea pigs did not cause irritation. However, repeated applications of Methyl Salicylate to guinea pigs caused scaling, dryness, and isolated and multiple infiltrates by day 4-6. Threshold changes were noted with application of a 50% oil solution. Concentrations of 10 and 25% did not cause any changes.

Tridecyl Salicylate

The dermal irritation potential of Tridecyl Salicylate was determined using six female Dunkin-Hartley albino guinea pigs (Vevy Europe, 1973d.) A dose of 500 mg/site was applied to intact and abraded dorsal skin on each animal. Tridecyl Salicylate was not irritating to guinea pig skin.

The dermal irritation potential was also determined using six male New Zealand white rabbits using the same dose and procedure (Vevy Europe, 1973e). The average PII was 0.195; Tridecyl Salicylate was not irritating to rabbit skin.

SENSITIZATION

Salicylic Acid

A local lymph node assay (LLNA) was performed in which groups of five CBA/J mice were dosed once daily for 4 consecutive days on each side of both external ears with 12.5 µl of 1, 10, or 20% Salicylic Acid in acetone (total of 25 µl/ear) (Gerberick et al., 1992). [^{3}H]TdR, 20 µCi, in phosphate-buffered saline (PBS) was injected i.v. 18-24 h after the fourth dose. The bilateral auricular lymph nodes were excised from each animal and pooled. Concentrations of 1, 10, and 20% Salicylic Acid produced 0.9, 1.8,and 7.2-fold increases; a positive response is a ≥2-fold increase that is significantly different than control values. (This was obtained with 20% Salicylic Acid.)

Boussiquet-Leroux et al. (1995) reported results of an LLNA performed using 5-20% Salicylic Acid dissolved 4:1 in acetone-olive oil (AOO). Groups of four female CD1 mice were dosed on the dorsum of the external ears with 25 µl of the test solution or the vehicle once daily on days 1-3. On day 5, the animal were given an i.p. injection of 100 mg/kg bromodeoxyuridine (BrdU) and killed after 2 h. A test also was performed that involved a pre-exposure procedure. An occlusive patch of 5-20% Salicylic Acid or vehicle was applied to the flank of groups of four mice for 48 h. Topical application was made to the external ears on days 6, 7, and 8, and on day 9, the animals were given an i.p. injection of BrdU and killed after 5 h.

Significant T-cell proliferation was observed, with a maximum treated versus control (T/C) ratio of 1.74. No cortical lymphocyte proliferation was noted. Very slight paracortical hyperplasia was sometimes observed, but generally, no remarkable effects were seen in the cortex.

Butyloctyl Salicylate

A guinea pig maximization test was performed to determine the sensitization potential of Butyloctyl Salicylate (Huntingdon Life Sciences, 1998d). Induction concentrations were 5% in propylene glycol given intradermally and 100% Butyloctyl Salicylate applied topically. The challenge was performed 14 days after the last induction dose. Patches of 50 and 100% Butyloctyl Salicylate were applied to two separate sites. Five male guinea pigs, which were used as an irritation control group, were treated concurrently during induction with propylene glycol and Freund's complete adjuvant/water emulsion and in the same manner as the test animals during challenge.

During induction, the test sites were evaluated 24 h after dosing and during challenge, the sites were evaluated 24 and 48 h after patch removal. None of the animals challenged with 100% Butyloctyl Salicylate had a sensitization response. The "severity indices" at 24 and 48 h were 0.4 and 0.2, respectively, for the test group and 0.6 and 0.3, respectively, for the irritation control group. One of 10 animals challenged with 50% Butyloctyl Salicylate had a clear dermal response. The "severity indices" at 24 and 48 h were 0.3 and 0.4, respectively, for the test group and 0.0 and 0.1, respectively, for the irritation control group.

Ethylhexyl Salicylate

The sensitization potential of Ethylhexyl (Octyl) Salicylate was determined in a maximization test performed using guinea pigs following OECD Test Guideline No. 406 (Haarmann and Reimer, 1991). Induction concentrations were 2.5% in arachis oil

given intradermally and 50% in ethanol/DEP (1:1) applied topically. At challenge, a 25% solution in ethanol/DEP (1:1) was used. Ethylhexyl (Octyl) Salicylate was not a sensitizer in guinea pigs.

Methyl Salicylate

A modified Magnusson-Kligman guinea pig maximization test was performed using Dunkin/ Hartley albino guinea pigs to evaluate the sensitization potential of Methyl Salicylate (Kimber et al., 1991). Ten animals were given a series of six intradermal injections of 2.5% Methyl Salicylate in 0.01% dodecyl benzene sulfonate/ saline and Freund's complete adjuvant in the shoulder region. After 6-8 days, an occlusive patch containing undiluted Methyl Salicylate was applied to the injection site for 48 h. A group of four animals was treated with vehicle only. A challenge was performed 12-14 days later by applying an occlusive patch containing 10% Methyl Salicylate in acetone/PEG 400 (70:30) for 24 h to a previously untested site on the clipped flank of each animal. The sites were scored after 24 h. Methyl Salicylate was not a sensitizer.

An interlaboratory trial of the murine LLNA was performed with Methyl Salicylate in AOO (Kimber et al., 1991). Groups of four CBA/Ca mice were exposed on the dorsum of both ears to 25 µl of 1, 2.5, or 5% Methyl Salicylate or vehicle daily for 3 consecutive days. Four days after the initiation of treatment, the animals were given an i.v. injection of 20 µl PBS containing 20 µCi of ^{3}H-TdR (2 Ci/mmol). The animals were killed 5 h after the injection, and the draining auricular lymph nodes were excised and the data pooled for each group. No positive response was observed with Methyl Salicylate. (A positive response is a >3-fold increase [stimulation index of 3] in ^{3}H-TdR incorporation as compared to the vehicle)

A guinea pig maximization study was performed to determine the sensitization potential of Methyl Salicylate (Basketter and Scholes, 1992). Albino Dunkin-Hartley guinea pigs (approximately 350 g) were used. A series of six intradermal injections of 2.5% Methyl Salicylate (in 0.9% NaCl aided by acetone) were followed after 6-8 days with a 48 h occluded patch using Methyl Salicylate at 100% and then 12-14 days later with a challenge on one flank with a 24 h occluded patch at the maximum non-irritant concentration (10%) in acetone/PEG 400 (70:30). No responses were seen at challenge and Methyl Salicylate was not a sensitizer.

An LLNA was performed in which groups of five CBA/J mice were dosed once daily for 4 consecutive days on each side of both external ears with 12.5 µl of 1, 2.5, or 5% Methyl Salicylate in acetone (total of 25 µl/ear) (Gerberick et al., 1992). [^{3}H]TdR, 20 µCi, in PBS was injected i.v. 18-24 h after the fourth dose. The bilateral auricular lymph nodes were excised and pooled for each animal. Doses of 1-5 % Methyl Salicylate all resulted in a 0.8-fold increase, which is a negative response.

In an LLNA following the same procedure as Kimber et al. (1991), with the exception that the animals were injected with ^{3}H-TdR and killed 4-5 days after the first application, Basketter and Scholes (1992) examined the sensitization potential of 5, 10,and 25% Methyl Salicylate in AOO. Methyl Salicylate was negative.

Another LLNA was performed following the same protocol, with the exception that the animals were injected with ^{3}H-TdR and killed 5 days after the first application (Basketter et al., 1994). Methyl Salicylate, tested at concentrations of 5, 10, and 25% in AOO, was negative.

Additional murine LLNA tests using female CBA/Ca or CBA/J mice were performed with Methyl Salicylate in AOO using standard and modified procedures in a number of laboratories (Kimber et al., 1995). One modification involved treatment for 4 days, the lymph nodes were excised 4 days after the initiation of dosing, and lymph node analysis was pooled from individual animals. A second modification involved the use of [^{125}I]iododeoxy-uridine (^{125}I-UdR) and the analysis of pooled data from individual animals. In the standard assay, 1-20% Methyl Salicylate produced no positive responses. Using the first modification, while a stimulation index of 3 was not observed, significant differences among individual mice were observed for test animals as compared to controls with 20% Methyl Salicylate.

Female Wistar and Brown Norway rats were used in a LLNA with 5-25% Methyl Salicylate (Arts et al., 1997). Serum IgE responses were also evaluated by applying 25% Methyl Salicylate to the shaved flank of Wistar and Brown Norway rats, followed by application of 12.5% to the dorsum of the external ear 7 days later. Methyl Salicylate did not cause a reaction in the LLNA; local lymph node weight and proliferation was actually decreased. Methyl Salicylate did not alter serum IgE response.

PHOTOSENSITIZATION

Salicylic Acid

The contact photosensitization potential of Salicylic Acid was determined using groups of five female albino outbred ICR mice (Miyachi and Takigawa, 1983). On days 0 and 1, 50 µl Salicylic Acid in acetone (believed to be at a concentration of 50%) was applied to the clipped abdominal skin of each animal, and the site was irradiated for 2.5 h at a distance of 15 cm. The irradiation source, a black light emitting UVA between 320-440 nm with a peak emission of 360 nm, consisted of three tubes in parallel arrangement with energy output at 15 cm of 2.7 mW/cm^2 at 360 nm and 0.17 mW/cm^2 at 305 nm (UVB); a glass filter was not used to limit UVB exposure. Control animals were dosed with vehicle and irradiated.

Prior to challenge, the ear thickness of all animals was measured. On day 5, the animals were challenged on both sides of the pinna with 20 µl Salicylic Acid in alcohol (believed to be at a concentration of 25%) followed by irradiation for 2.5 h at a distance of 15 cm. Ear thickness was measured at the peak time of ear swelling, i.e. 24 h after challenge. Some animals were pretreated by i.p. injection of 20, 100, or 200 mg/kg cyclophosphamide to enhance delayed-type hypersensitivity. Salicylic Acid was not a photosensitizer.

Tridecyl Salicylate

Ten male Hartley albino guinea pigs were used to determine the phototoxic potential of Tridecyl Salicylate (Biolab, 1998b). During induction, 0.5 ml of 2% Tridecyl Salicylate in dehydrated alcohol was applied to a shaved area of the back and massaged in three times daily for 2 wks (Monday-Friday). The test sites were then irradiated with UVA + UVB, emission spectrum between 285 and 350 nm, for 15 min at a distance of approximately 30 cm. The challenge was performed 14 days after the last UV exposure. One-half ml of 0.1% Tridecyl Salicylate in dehydrated alcohol was applied once, and the site was irradiated. The test sites were examined 24, 48, and 72 h after the challenge. A control group of five animals was treated with dehydrated alcohol only. No erythema or edema was observed in test or control animals. Tridecyl Salicylate was not a photosensitizer.

OCULAR IRRITATION

Butyloctyl Salicylate

The ocular irritation potential of Butyloctyl Salicylate was determined according to FHSA methods (Leberco•Celsis Testing, 1996c). Butyloctyl Salicylate produced minimal conjunctival irritation in three of six animals; all eyes were normal by day 3. Butyloctyl Salicylate was not a primary ocular irritant according to the FHSA.

Ethylhexyl Salicylate

The ocular irritation of a 50% solution of Ethylhexyl (Octyl) Salicylate in DEP was studied using rabbits following OECD Test Guideline No. 405 (Haarmann and Reimer, 1991). The 50% solution of Ethylhexyl (Octyl) Salicylate was non-irritating to rabbit eyes.

Isodecyl Salicylate

The ocular irritation potential of Isodecyl Salicylate was determined using six male New Zealand albino rabbits (Vevy Europe, 1973f). One-tenth ml containing a dose of 10 mg of the test material (at a concentration of 10% (v/v) in liquid paraffin) was instilled into the conjunctival sac of each animal, and the eye was not rinsed. No irritation was observed at any time. The researchers concluded that Isodecyl Salicylate was not an ocular irritant at the dilution tested.

Methyl Salicylate

Methyl Salicylate was severely irritating to guinea pig eyes (Opdyke, 1978). However, Rumyantsev et al. (1992) reported that Methyl Salicylate was not irritating to rabbit eyes.

Tridecyl Salicylate

One-tenth ml of undiluted Tridecyl Salicylate was instilled into the conjunctival sac of the right eye of three male New Zealand white rabbits, and the ocular irritation was determined (Biolab, 1998c). The contralateral eye served as a control. The eyes were examined 1, 24, 48, and 72 h and 7 days after instillation. In all animals 60 min after instillation, "congestion without chemosis" was observed; this lesion was not present in two animals 48 h after instillation nor in the remaining animal 7 days after instillation. No other effects were observed. The researchers concluded that

Tridecyl Salicylate was non-irritating to rabbit eyes.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Salicylic Acid, produced when aspirin is rapidly hydrolyzed to Salicylic Acid after absorption from the gut, was reported to be the causative agent in aspirin teratogenesis in rats by Kimmel et al., (1971).

IN VITRO STUDIES

A number of *in vitro* teratogenicity studies have been performed on salicylates, all generally having positive results. Some were mechanistic and examined whether teratogenic effects were due to aspirin or Salicylic Acid (Yokoyama et al., 1984) or due to salicylate or its metabolites (Greenaway et al., 1984).

The effect of Salicylic Acid on nervous system development was studied (Khera and Whalen, 1988; Joschko et al., 1993), and the overall teratogenic potential of Salicylic Acid (Mummery et al., 1984) and Sodium Salicylate was examined (McGarrity et al., 1981; Greenaway et al., 1982; Flint et al., 1984; Ebron-McCoy, 1988; Akita et al., 1995).

The effect of Salicylic Acid on human spermatozoa was determined following incubation with 50, 100, or 200 mg/l salicylate for 2-48 h (Porat-Soldin and Soldin, 1992). A dose-response effect was observed with significant inhibition of motility at all times, and the inhibition was significantly increased with time. The decrease was in sperm motility and not due to sperm death.

IN VIVO DERMAL STUDIES

Methyl Salicylate

Methyl Salicylate (350 and 525 mg/100 g was applied to the skin of the backs and delivered by oral intubation (1.75 g/kg) of timed-pregnant LVG hamsters (approximately 100 g body weight) at 7 d 9 h of gestation (Overman and White, 1983). The incorporated dose was measured using spectrophotometric analysis of blood salicylate concentrations. Blood levels reached a peak of 125 mg/100 ml at about 2 h after oral treatment. A peak salicylate level of 50 mg/100 ml was obtained 5-6 h after topical application of 350 mg/100 g and a peak of 120 mg/100 ml with the 525 mg/100 g topical treatment level. The high topical dose level, however, was not well tolerated and was discontinued. Most embryos were removed at 9 d of gestation. Of those that were allowed to develop, few survived beyond 12 d of gestation.

Malformations at 9 d of gestation were used as an indicator to teratogenic effect. Of 35 litters (fetuses per litter not given) in the oral treatment group, 72% of the fetuses had neural tube defects. Of 6 litters (number of fetuses per litter not given) produced by animals given the low topical dose, 6% of the fetuses had neural tube defects; and of 19 litters in the high topical dose group, there were 53% neural tube defects. The researchers stated that these results are consistent with the blood salicylate concentrations.

The teratogenic potential of a petroleum-based grease manufactured using 3% Methyl Salicylate was determined using rats (Infurna et al., 1990). The test material was applied dermally to groups of 12 gravid animals at a dose of 1, 3, or 6 g/kg/day on days 6-15 of gestation. A positive control group was dosed dermally with 2 g/kg/day undiluted Methyl Salicylate; the dose was reduced to 1 g/kg/day on days 10-15 of gestation because of maternal toxicity (i.e., 25% mortality and severe dermal irritation). A negative control group was also used.

In the test groups, no maternal toxicity was observed. No changes in reproductive parameters and no malformations or variation attributable to dosing were observed. Positive control animals had 100% incidence of total resorptions. Urinalysis reported "very high concentrations" of Salicylic Acid in the urine of the positive control animals and that a "significant proportion" of the available Methyl Salicylate was absorbed from the test material. However, the urinary concentrations of Salicylic Acid in the test animals were "far below the toxic levels" observed in the positive controls.

IN VIVO ORAL STUDIES

Salicylic Acid

Groups of 20 gravid Wistar rats were fed a diet containing 0.06, 0.1, 0.2, or 0.4% Salicylic Acid - on days 8-14 of gestation (Tanaka et al., 1973a). The control group was given a basal diet. On day 20 of gestation, 15 of the animals of each group were killed; the remaining five were allowed to deliver. The offspring, which were weaned on day 21, were observed daily and weighed every 3 days. Offspring were killed and autopsied on the 56th day for examinations of visceral and skeletal abnormalities.

Maternal weight loss was marked for animals of the 0.4% group with initial dosing, but a gradual weight gain was observed after day 11. Maternal weight loss correlated with a decrease in feed and water consumption. Salivation and/or piloerection were observed in this group. All dams survived until study termination.

Uterine and placental weights were significantly decreased in animals of the 0.4% group as compared to controls; this groups had 71.2% neonatal mortality. The ratios of resorptions, placental remnants, and implantation sites to the number of implantations were 23.9, 31.4, and 15.9%, respectively. Litter size was significantly decreased in the 0.4% group; body weight, body length, and tail length of offspring were significantly decreased in the 0.2 and 0.4% groups, and tail length was significantly decreased in the 0.1% group. The effects seen in offspring (determined at autopsy on the 56th day) were 3.8% external anomalies, no internal organ anomalies, and 14.6% skeletal anomalies for the 0.2% group; and 29.6% external anomalies, 13.6 internal organ anomalies, and 46.8% skeletal anomalies for the 0.4% group.

In the 0.4% group, one dam gave birth to six live offspring, but all six offspring died within 1 day; none of the other dams in this group gave birth to live offspring. Male and female offspring from animals of the 0.1% group had decreased body weights, body length, and tail length compared to controls.

In male offspring, again at autopsy on the 56th day, a significant increase in spleen weight was observed for the 0.06% group, a significant increase in carcass, heart, kidney, adrenal gland, and testis weights were observed for the 0.1% group, and a significant increase in kidney weights and a significant decrease in lung weights was observed for the 0.2% group compared to controls.

In female offspring at autopsy on the 56th day, a significant increase in carcass and ovary weights was observed for the 0.06% group and a significant increase in carcass, liver, adrenal gland, and ovary weights was observed for the 0.1% group compared to controls. The incidence of skeletal anomalies determined at the 56th day in offspring of the 0.2% group was 13.8%; skeletal anomalies were not observed in the other groups, and no external or internal organ anomalies were seen in the 0.06-0.2% groups.

Groups of 20 gravid Wistar rats were dosed orally with 75, 150, or 300 mg/kg Salicylic Acid in a 0.5% solution of sodium carboxymethylcellulose once daily on days 8-14 of gestation (Tanaka et al., 1973b). The control group was given 5 ml/kg of vehicle. On day 20 of gestation, 15 of the animals of each group were killed; the remaining five were allowed to deliver. The offspring, which were weaned on day 21, were observed daily and weighed every 3 days. Offspring were killed and autopsied on the 56th day for examinations of visceral and skeletal abnormalities.

Maternal body weight gain was inhibited for animals of the 300 mg/kg group. Salivation and/or piloerection were observed in this group. Feed and water consumption decreased during the administation of 300 mg/kg Salicylic Acid. Three animals of this group died within a few days of the initiation of dosing. Decreased uterine weight was observed in animals of the 150 and 300 mg/kg dose groups as compared to controls; these groups had 25.7 and 100% fetal mortality, respectively. Litter size and neonatal body weight, body length, and tail length were significantly decreased in the 150 mg/kg dose group. The incidences of external, internal, and skeletal anomalies in offspring autopsied at the 56th day were 1.8, 0, and 2.5%, respectively, for the 75 mg/kg group and 27.8, 12.7, and 65.7%, respectively, for the 150 mg/kg group.

The offspring from animals of 150 mg/kg Salicylic Acid group had decreased body length and tail length compared to controls. The thyroid weight of male offspring from the 75 mg/kg group was significantly increased and the adrenal gland weight of male offspring from the 150 mg/kg

group was significantly decreased compared to controls. The incidences of external organ, internal organ, and skeletal anomalies in offspring were 0, 5.0, and 0%, respectively, for the 75 mg/kg group and 13.7, 17.2, and 79.2%, respectively, for the 150 mg/kg group.

Waltman et al. (1973) studied the effects of anti-inflammatory drugs on parturition parameters in the rat. Groups of 10 gravid Sprague-Dawley rats were orally given 10 mg/kg Salicylic Acid twice daily on days 20 and 21 of gestation (Waltman et al., 1973). Control groups were either untreated or given 2.0 ml distilled water on the same days. The animals were observed daily until day 20; after the first dose, the animals were observed every 2 h until delivering. Time of onset of parturition, duration of parturition, bleeding during parturition, and perinatal mortality were noted. Salicylic Acid significantly increased time of onset of parturition compared to controls. The duration of parturition was increased in only one animal. Bleeding at parturition was increased in four animals as compared to controls. None of the 106 pups born to these 10 animals were dead (compared to 4 of 109 pups in the control group).

Methyl Salicylate

In a reproduction study, groups of 25 male and 25 female mice (F_0 generation) were fed a diet containing 0.25 or 0.5% Methyl Salicylate for 30 days prior to mating (Abbott and Harrisson, no date). A negative control group was fed untreated diet. The F_0 animals were mated twice to produce F_{1a} and F_{1b} litters. The F_{1a} litter was maintained through weaning, while 30 males and 30 females were chosen from the F_{1b} litter to parent the F_{2a} and F_{2b} litters. All animals were fed the appropriate diet from study initiation through weaning of the F_{2b} litters. All litters were culled to 10 neonates at day 5.

Results only included data from females in each generation that were available for two successive mating. No gross abnormalities were observed for neonates of any litter, and all surviving to weaning were normal in growth, appearance, and behavior. Conception rate, the number of unsuccessful matings for females, and the number of stillbirths were greater for the negative controls than the test groups. Litter size was slightly smaller in the test groups than the control, but the neonate death rate between birth and weaning was lower than controls. Viability, lactation, and reproduction indices of the test groups were comparable to greater than those of the controls.

A reproduction study using 25 male and 25 female Wistar rats was performed following the same protocol, with the exception that the animals were fed a diet containing 0.25 or 0.5% Methyl Salicylate for 60 days prior to mating (Abbott and Harrisson, no date). No gross abnormalities were observed for neonates of any litter, and all surviving to weaning were normal in respect to growth, appearance, and behavior. The mating performance, reproduction indices, and viability indices were decreased in the 0.5% group compared to the other groups. Litter size was consistently decreased for the two test groups compared to controls, and the number of deaths between birth and day 5 was greater in the 0.5% group than in the control or 0.25% groups.

Groups of gravid CD rats were dosed (route not specified) with 0.05 or 0.1 ml Methyl Salicylate on days 10 and 11 of gestation, and either killed on day 21 of gestation or allowed to deliver (Woo and Hoar, 1972). A control group was not treated. Test animals of the 0.1 ml group had decreased body weight gain, fewer and smaller neonates, and more resorptions and malformed neonates. The kidneys of gestation day 21 fetuses and postnatal day 1, 6, 12, and 24 fetuses were examined. Fetal kidney weight was decreased in the treated groups compared to the controls. Methyl Salicylate inhibited lengthening of the renal papilla, and treated fetuses had a significant increase in the incidence of kidneys without papillae. There was little or no difference in neonatal kidney weights between test and control animals by postnatal day 6.

Groups of 24-27 Sprague-Dawley rats were fed a diet containing 4000 or 6000 ppm Methyl Salicylate and U.S.P. calcium carbonate for 60 days prior to mating (FDA, 1966). The dams were fed the test diets until the neonates were weaned at day 20 or 21, and the procedure was repeated with a second mating. No abnormalities were observed in the offspring of test animals. Neonate survival at weaning was greater in the test groups than in the control group.

The reproductive effects of Methyl Salicylate were determined in a three-generation study using Osborne-Mendel rats (Collins et al., 1971). Concentrations of 500, 1500, 3000, and 5000 ppm synthetic Methyl Salicylate were mixed with chow and fed to groups of 10 males and 10 fe-

males *ad libitum*. Controls were given untreated chow. After 100 days of dosing, the animals (F_0 generation) were mated. Reproductive parameters were measured for the first litter (F_{1a}); these animals were killed at weaning. The F_0 parents were remated, and reproductive parameters were measured for the F_{1b} litter; 20 littermated pairs were selected to parent the next generation. The procedure was repeated for succeeding generations until the animals of the third generation were killed and necropsied. The effects on reproductive parameters are summarized in Table 9.

Gravid LVG hamsters were dosed orally with 175 mg/100 g at 7 days 9 h of gestation (Overman and White, 1983). Controls were dosed with saline solution. Fetuses were recovered on day 9 of gestation. Plasma salicylate concentrations were determined. In 35 litters, 72% had neural tube defects. The plasma salicylate concentration peaked at 125 mg/100 ml 2 h after dosing and returned to control values within 8-10 h. Testing showed that salicylate was reaching the fetus.

Morrissey et al. (1989) reported on the results of 48 chemicals (including Methyl Salicylate) tested in the National Toxicology Program's Reproductive Assessment by Continuous Breeding (RACB) study using Swiss CD-1 mice. The study protocol begins with a 14-day dose ranging study (Task 1), followed by the continuous breeding phase (Task 2). In Task 2, the animals were dosed for 7 days prior to mating and then during 98 days of mating and cohabitation. Task 3 is crossover mating, and Task 4 is the second generation. In Task 4, animal were reared by dams until weaning (postnatal day 21) and then dosed until mating at postnatal day 74. Task 2 used three treatment groups (20 animals per sex per group) and a control (40 animals per sex). Task 4 used the last litter in Task 2 from the control and the high dose group. Methyl Salicylate in corn oil was tested simultaneously in two laboratories. In one laboratory, doses were 25, 50, and 100 mg/kg/day by gavage (Research Triangle Institute, 1984). In the other laboratory, the three doses were 100, 200, and 500 mg/kg/day (Environmental Health Research Testing, Inc., 1984). In both studies, corn oil alone served as the control. The RACB using 100-500 mg/kg/day found a decrease in live pups per litter, the percentage of live pups, and pup weight at 500 mg/kg/day. The RACB using 25-100 mg/kg/day found no effect on these parameters.

Lamb et al. (1997a, 1997b) further reported on these studies. In the RACB using 25-100 mg/kg/day (Lamb, 1997a), the last control group and 100 mg/kg/day group litters were dosed with Methyl Salicylate (100 mg/kg/day) until a Task 4 mating as described above. There were no Methyl Salicylate related changes in the number of pups per litter, the percentage of live pups, or pup weight. The F_1 adults were necropsied and no effects were found on body or organ weights, and the motility, density, and morphological endpoints for sperm were normal.

Lamb et al. (1997b) further described results from the 100-500 mg/kg/day study, confirming the findings reported in Morrissey et al. (1989), but also indicating a 3% reduced pup weight for the 250 mg/kg/day dose group not reported in Morrissey et al. (1989). In an attempt to define the affected sex which led to positive reproductive toxicity findings in this study, a Task 3 crossover mating was done using the control and 500 mg/kg/day dose group. There were no discernable effects.

Sodium Salicylate

Groups of two CFE rats were given a single oral dose of 500 mg/kg Sodium Salicylate in 0.9% saline on day 8 of gestation or daily doses of 100 mg/kg Sodium Salicylate on days 7-11 of gestation; the animals were killed on day 15 or 19 (Lansdown et al., 1970). Controls were given vehicle only. A single dose of 500 mg/kg resulted in 50% maternal toxicity. With this dose, the incidence of resorptions and dead fetuses was 53% and the incidence of malformations was 13%. None of the animals dosed over 5 days died. With this dosing regimen, the incidence of resorptions and dead fetuses was 15%; no malformations were seen. Aberrations in skeletal preosseous cartilage, particularly the cartilage matrix, were observed. The authors concluded that the findings suggest an inhibition of muco-polysaccharide synthesis during skeletal development.

Twenty-five gravid A/Jax mice were given a single oral dose of 66.6 mg/ml Sodium Salicylate in 1% sodium carboxymethylcellulose at a volume of 0.2 ml/20 g body wt on day 17 of gestation, and a control group was dosed with vehicle only (Eriksson, 1971). Five of the animals were killed 4 h after dosing and at least five

Table 9. Effects of Methyl Salicylate on Reproductive Parameters in Rats (Collins et al., 1971)

Reproductive Parameter	Animals Affected
Fertility Index	No significant differences for any dose/1st generation; "appreciable decreases seen in 2nd and 3rd generations/5000 ppm
Avg Litter Size/Female	Significant decreases in 2nd generation/2nd mating/3000 ppm; significant decreases in 2nd generation/both matings/5000 ppm; decreases seen in 2nd generation/ 1500 ppm were not significant because of the large variation in progeny between females
Avg # Liveborn Pups/Female	Significant decreases in 2nd generation/both matings/3000 & 5000 ppm
Viability Index	"Possible loss of young through stillbirths" in 2 matings/5000 ppm
Avg # Surviving Progeny/Female Day 4	Significant decreases in 2nd generation/both matings/3000 & 5000ppm
Survival Index Day 4	Adverse effect in 2nd generation/3000 & 5000 ppm and 3rd generation/1st mating/3000 & 5000 ppm
Avg # Progeny Weaned/Female Day 21	Significant decrease in 2nd generation/1st mating/3000 ppm; significant decrease in 2nd generation/both matings/5000 ppm
Weaning Index	"Appreciable decrease" in 2nd generation/2nd litter/5000 ppm
Avg weanling Wt - Day 21	Consistent decreases/3000 & 5000 ppm
External Examination	No grossly visible abnormalities
Necropsy - 3rd Generation Weanlings	Negative findings, including microscopic examination of livers and kidneys of weanlings of control, 3000 and 5000 ppm groups

fetuses per litter were used for hepatic glycogen determination. The remaining 20 dams were killed 24 h after dosing; one of the 20 delivered prior to being killed. In the animals killed 24 h after dosing, fetal mortality was 47% and the incidence of superficial, hepatic, and gastric hemorrhage was 6, 1, and 2%, respectively. Carboxymethylcellulose significantly decreased fetal hepatic glycogen, and dosing with Sodium Salicylate further decreased glycogen in a significant manner.

As described earlier, Waltman et al. (1973) studied the effects of anti-inflammatory drugs on parturition parameters in the rat. The results below were obtained in rats given 10 mg/kg Sodium Salicylate orally twice daily on days 20 and 21 of gestation. Time of onset of parturition, duration of parturition, bleeding during parturition, and perinatal mortality were noted. Sodium Salicylate had no significant effect on the time of onset of parturation compared to controls. The duration of parturition was increased in only 5 animals compared to controls. Bleeding at parturition was increased in five animals as compared to controls. Thirteen of the 121 pups born to these 10 animals were dead (compared to 4 of 109 pups in the control group).

Two groups of 21 gravid albino rats were dosed orally with 200 mg/kg Sodium Salicylate once daily on days 6-15 of gestation (Keplinger et al., 1974). Three control groups of 16-21 gravid rats were given 1.5% aq. methylcellulose (vehicle) only. All animals were killed on day 20 of gestation.

In the second test group, a significant increase was observed in the number of resorption sites and the total number of females with one or more resorption sites (71.4%); the number of viable fetuses was significantly decreased in this group. No significant reproductive effects were observed in the first test group. Regarding fetal development, the number of fetuses with skeletal abnormalities was significantly increased in both test groups (67.8 and 75.9% in test groups 1 and 2, respectively) as compared to controls; the number of fetuses with external and internal abnormalities was significantly increased in the second test group (6.2 and 45.3%, respectively) but not in the first test group.

A group of 22 gravid CD-1 mice was dosed orally with 800 mg/kg once daily on days 8-12 of gestation (Chernoff and Kavlock, 1982; 1983). A control group of 21 gravid mice was dosed with water only. All animals were allowed to deliver. Average neonatal weight, measured on days 1 and 3 of parturition, was decreased in test - neonates as compared to controls.

Groups of gravid Sprague-Dawley and Long-Evans rats were dosed orally with 125 or 175 mg/kg Sodium Salicylate on days 8-10 of gestation; a control group was dosed with distilled water (Buelke-Sam et al., 1984). The litters were culled to eight neonates on postnatal day 1 and weaned on day 21. Locomotor activity was tested for 30 min in the dark on days 12, 16, 20, 24, 30, 60, 90, and 120 using both clean bedding and homecage bedding. Dosing did not affect maternal weight gain or length of gestation.

No malformations were noted in the neonates, and there were no significant differences in body weights on day 1.

Male offspring had more salicylate-related activity changes compared to female offspring. Male Long-Evans test rats were less active than controls on test days 30+. Regarding dose and age interaction, the activity level was significantly decreased on days 20, 30, and 60 in high dose male Long-Evans rats tested over homecage bedding, increased on day 12 and decreased on day 30 in Long-Evans female rats tested over clean bedding, increased on days 20 and 24 in low dose male Sprague-Dawley rats tested over clean bedding, and increased on days 24, 30, and 90 in high dose male Sprague-Dawley rats tested over clean bedding. The researchers concluded that the alterations in activity "were the result of a complex interaction among dose, strain, offspring, sex and bedding condition during testing."

Gravid New Zealand White rabbits were dosed orally with 100 mg/kg Sodium Salicylate in water on days 4-7 of gestation (Fabro et al., 1984). The animals were killed on either day 8 or 28 of gestation, and the number of implantations and corpora lutea or the incidence of malformations was determined, respectively. Sodium Salicylate did not affect the preimplantation ratio in animals killed at 8 or 28 days, and it did not affect the average litter size of viable offspring or induce teratogenic effects in animals killed at 28 days.

Groups of 12-15 gravid albino rats were orally given Sodium Salicylate in tap water at a volume of 1 ml/100 g body wt at a dose of 25, 75, or 150 mg/kg on days 15-20 of gestation or at a dose of 4.2, 12.5, or 25 mg/kg on days 20-21 of gestation (Fritz and Suter, 1985). The surviving neonates were weighed at various times through day 35, and behavioral tests were performed. The dams were killed after weaning and the neonates were killed on day 42.

Maternal body weight gain was comparable for all groups, and no signs of toxicity were observed. Parturition was delayed in one female of the control and 25 mg/kg group and two females of the 150 mg/kg group. Litter size and male-to-female ratios were similar for all groups. The neonatal mortality rate in the 150 mg/kg group dosed on days 15-20 and in the 12.5 and 25 mg/kg group dosed on days 20-21 was increased in a dose-dependent manner. Body weight gains were similar between groups. No development abnormalities were observed.

Gravid CD-1 mice were dosed orally with Sodium Salicylate in distilled water at a volume of 0.5 ml on day 8 of gestation; 19 animals were given 2000 mg/kg and 37 were given 2600 mg/kg Sodium Salicylate (Kavlock et al., 1985). A control group of 15 gravid animals was dosed with the vehicle. The animals were killed on day 18 of gestation. Maternal weight gain was significantly reduced in both test groups, and maternal mortality was 11 and 24% in the 2000 and 2600 mg/kg dose groups, respectively. Fetal weight was not affected.

The incidence of viable litters was 71 and 79% for the low and high dose groups, respectively. In one dam given 2600 mg/kg Sodium Salicylate, the whole litter was resorbed. The incidence of fetal mortality was 14 and 7% in the low and high dose groups, respectively, and 7% in the control group. The incidence of supernumerary ribs was significantly increased in fetuses of both test groups. However, in the 2000 mg/kg group, the number of fetal sternal ossifications was significantly decreased compared to controls. In the low dose group, 7% of the fetuses and 17% of the litters had malformations; in the high dose group, these values were 3 and 9%, respectively.

Groups of gravid CD-1 mice and Sprague-Dawley rats were dosed orally with 1500 and 300 mg/kg Sodium Salicylate in distilled water, respectively, on day 7, 8, 9, 10, or 11 of gestation; controls were dosed with vehicle (Beyer and Chernoff,

1986). The mice were killed on day 18 and the rats on day 21 of gestation.

Some of the mice died as a result of dosing; maternal toxicity was not seen in the surviving animals. Fetal weight gain was not affected, but fetal mortality was significantly increased with dosing on day 10. The number of extra ribs was significantly increased with dosing on days 8 and 9, and the combined effect of extra ribs and ossification sites was greater on day 9 than day 8. None of the rats died on study, and maternal toxicity was not seen. Fetal weight gain and the number of implantation sites was not affected by dosing. Extra ribs were induced significantly more with dosing on day 10 than any other day, and ossification sites were also seen more frequently. Cervical ribs were significantly increased with dosing on day 8.

A group of 30 gravid ICR/SIM mice were dosed orally with 1600 mg/kg Sodium Salicylate in distilled water on days 8-12 of gestation, and a control group of 30 gravid mice was given vehicle only (Seidenberg et al., 1986). All animals were allowed to deliver. Seven animals died as a result of dosing. Maternal weight gain was significantly decreased compared to controls. Percent neonate survival (96%) was significantly decreased compared to controls. The average number of viable neonates per litter was significantly decreased on days 1 and 3 of parturition and the number of dead neonates per litter was significantly increased on day 1. Average neonatal weight was similar to controls.

Groups of 17-19 gravid Sprague-Dawley rats were dosed orally with 30, 90, or 180 mg/kg Sodium Salicylate in distilled water on days 6-15 of gestation; a control group was dosed with vehicle only (Fritz and Giese, 1990). The dose volume was 1 ml/100 g. The animals were killed on day 21 of gestation. Some reduction in feed consumption was observed in the 180 mg/kg dose group. As indicated by decreased fetal body weight and retarded skeletal maturation, growth was dose-dependently decreased in the 90 and 180 mg/kg groups. Teratogenicity occurred at a rate of 0.7 and 30% in these groups, respectively. The most prominent malformation in the high dose group was cranio(rachi)schisis. In the mid dose group, no embryotoxicity or maternal toxicity was observed. In the high dose group, marked embryotoxicity and low maternal toxicity were observed.

Gravid Sprague-Dawley rats were dosed by gavage twice daily on days 15-21 of gestation with Sodium Salicylate to determine the effect on reproduction (Davis et al., 1996). Groups of 25 animals received 20 or 80 mg/kg/day and a group of 16 animals received 200 mg/kg/day Sodium Salicylate in 0.5% aq. methyl cellulose. One-half of the dose was administered in the morning and the other half was given 6-8 h later; dose volume was 10 ml/kg/"dosing occasion". A group of 16 gravid rats was dosed orally with 260 mg/kg/day acetylsalicylic acid (ASA) in methyl cellulose twice daily on days 15-21 of gestation. The animals were observed twice daily until day 21 of gestation; as of day 21, the animals were observed hourly for the onset of labor. Surviving F_0 dams and F_1 neonates were killed on day 1 of lactation.

The onset and the duration of labor were increased in animals dosed with 200 mg/kg Salicylic Acid and those dosed with ASA; the delay in the onset of labor in the Sodium Salicylate group was not statistically significant. A non-statistically significant increase in fetotoxicity and peripartum mortality was also observed for the 200 mg/kg Sodium Salicylate group; a significant increase in neonates born dead and peirpartum death was seen with ASA.

The researchers stated that "it is likely that the observed increased peripartum death of fetuses in these dose groups is associated with complications of prolonged labor, since those pups that did not survive delivery had no visible abnormalities or signs of overt toxicity. However, the pups were not examined for the development of hemorrhage." A statistically significant increase in maternal perinatal death was reported in animals of the 200 mg/kg Sodium Salicylate and ASA groups. A statistically significant decrease in gestational index was also observed as a result of increased maternal death.

IN VIVO PARENTERAL STUDIES

Salicylic Acid

A group of 17 gravid Sprague-Dawley rats was given a s.c. injection of 380 mg/kg Salicylic Acid on day 9 of gestation; the dose was injected in two equally divided doses 2 h apart (Koshakji and Schulert, 1973). A group of 15 controls was given deionized water. Immediately following the second dose, mineral isotopes of ^{54}Mn, ^{65}Zn (both

carrier free), and ^{59}Fe (27 mCi/mg) were given s.c. Urine was collected and assayed for mineral isotopes. The animals were killed on day 20 of gestation.

Effects of dosing included "loss of appetite, complete relaxation, weakness, drowsiness, muscular limpness, inactivity, accelerated respiration rate, and occasionally elevated water intake and urinary excretion." Marked maternal weight loss and death of one test animal were observed after dosing. In the test animals, mean fetal weight was significantly decreased compared to controls. Administration of Salicylic Acid resulted in 46.6% resorptions and in 5.3% of the viable fetuses being malformation. The researchers stated that "none of the other metabolites, derivatives or analogs of salicylic acid [that were also tested] resulted in fetal anomalies." Salicylic Acid did not affect the urinary excretion of ^{54}Mn, ^{59}Fe, or ^{65}Zn.

Groups of three or four gravid Sprague-Dawley rats were given a s.c. injection of 300 or 380 mg/kg ^{14}C-Salicylic Acid in two equal doses 2 h apart on day 16 of gestation followed by s.c. injection of ^{54}Mn, ^{59}Fe, and ^{65}Zn (Koshakji and Schulert, 1973). The animals were killed 6 or 24 h after dosing. Salicylic Acid did not affect the maternal-fetal uptake of the minerals. An increased ^{65}Zn content in the liver 6 h after administration was the only difference observed compared to control values. Administration of 380 mg/kg Salicylic Acid on day 16 of gestation resulted in three incidents of hematuria, a "high rate" of fetal mortality, and superficial hemorrhage which was occasionally observed along the brain and spine.

Methyl Salicylate

Gravid female rats were given a single s.c. dose of 0.1-0.5 cc Methyl Salicylate on day 9, 10, or 11 of gestation (Warkany and Takacs, 1959). Twenty-six dams died and 47 resorbed their fetuses. The remaining 43 dams were killed on day 21 of gestation. External abnormalities were seen in 45 of 298 fetuses. Skeletal anomalies were seen in 75 of 253 fetuses which appeared externally normal. No information was provided as a function of dose.

The effect of fetal growth retardation on organ differentiation was examined using groups of five gravid CD rats (Kavlock et al., 1982). The animals were dosed i.p. with 200 or 400 mg/kg Methyl Salicylate on days 8-9 and killed on day 20 of gestation. A negative control group was used.

Embryotoxicity was observed in the high dose group. Average fetal mortality was 2 and 50% for the 200 and 400 mg/kg groups, respectively. In the 200 mg/kg group, one fetus had a diaphragmatic hernia and two had encephalocele. In the 400 mg/kg group, one incidence each of cleft palate and hydrocephaly and two incidences each of encephalocele, gastroschisis, and spina bifida were observed. The fetal body weight index was significantly reduced in the 400 mg/kg group, with a delay of 0.96 day. Dose-related reductions were observed in brain weight, lung growth, hepatic growth, and renal weight. The reduction in kidney development was related to growth retardation.

In a study to determine the effect of Methyl Salicylate on renal function, groups of five to 16 gravid Sprague-Dawley rats were dosed i.p. with 250-450 mg/kg on day 11, 200-300 mg/kg on days 10-11, 300-375 mg/kg on days 11-12, or 200-300 mg/kg Methyl Salicylate on days 11-13 of gestation (Daston et al., 1988). A control groups was dosed with 5 ml/kg 0.85% saline on days 10-13 of gestation. All animals were killed on day 20 of gestation. Maternal toxicity was observed in many of the dose groups, and a few, non-dose-related, maternal deaths occurred.

Malformations were observed in fetuses of groups dosed with $\geq$350 mg/kg on day 11 of gestation or with $\geq$300 mg/kg on more than one day. The incidence of resorptions was significant in the 400 mg/kg group dosed on day 11 of gestation. Fetal weight was significantly reduced in a dose-related manner. Methyl Salicylate did affect kidney development, but there was no relationship between the incidence of dilated renal pelvis and Methyl Salicylate.

Daston et al. (1988) also dosed gravid Sprague-Dawley rats i.p. with 200, 250, or 300 mg/kg Methyl Salicylate on days 10-13 of gestation. A high incidence of maternal mortality was seen in the 300 mg/kg dose group. During postnatal days 1-2, neonate mortality was increased in the 250 and 300 mg/kg groups; no external abnormalities were seen in the surviving pups, and weights were similar to control values. No effect on average litter size or birth weight was observed in the 200 mg/kg group. Relative kidney weights were significantly increased in all test groups on

postnatal day 15; however, no difference was seen at wk 4. Renal defects were "rarely observed". Neonatal urinary parameters were not affected by prenatal dosing with Methyl Salicylate, but some effect on the urine concentrating ability was seen in young neonates.

Sodium Salicylate

Jackson (1948) examined the effect of Sodium Salicylate on gravid rats and rabbits. Groups of one to five rats were given a single s.c. dose of 0.20-0.75 g/kg Sodium Salicylate during the last week of pregnancy, and the animals were killed 2 days later. The maternal death rate was 2/5 and 3/3 animals of the 0.50 and 0.75 dose groups, respectively. In the surviving animals, all the fetuses survived. Using gravid rabbits, four were dosed s.c. with 0.5 and two with 1.0 g/kg Sodium Salicylate as a single dose during the last week of pregnancy, and again the animals were killed 2 days later. All of the animals of the 1.0 g/kg and one of the animals of the 0.5 g/kg dose group died. Of a total of 23 fetuses in the surviving rabbits, 19 survived.

Gravid female rats were given a single s.c. dose of 60-180 mg Sodium Salicylate on day 9, 10, or 11 of gestation (Warkany and Takacs, 1959). Six dams dosed with >120 mg died (no other information given as a function of dose); 24 animals resorbed their fetuses. Thirteen surviving animals were pregnant on day 21 of gestation, at which time the animals were killed. External abnormalities were seen in 15 of 100 fetuses, and skeletal anomalies were seen in 11 of the 85 fetuses that appeared externally normal.

Groups of nine to 42 gravid Sprague-Dawley rats, housed three per cage, were dosed s.c. with 200-500 mg/kg Sodium Salicylate on day 10 and killed on day 20 of gestation (Goldman and Yakovac, 1963). "Significant numbers" of anomalies were observed in fetuses of the 400 and 500 mg/kg dose groups.

Gravid A/Jax mice were given a single i.m. dose of 10 mg Sodium Salicylate in 0.1 ml distilled water on day 7, 8, 9, 10, 11 , 12, or 13 of gestation, and the animals were killed on day 18 (Larsson et al., 1963). "A high incidence of external anomalies" was observed in fetuses of animals dosed on day 12 or 13 of gestation. The "appearance of reddish-brown spots on the nose, chin, and paws", which was "a large mass of blood enclosed in a thin-walled capsule", was observed in a number of fetuses. A "high incidence of deformities of ribs and vertebrae" was observed in all dose groups.

Gravid A/Jax and CBA mice were given a single i.m. injection of 10 mg Sodium Salicylate in 0.1 ml distilled water on either day 9 or 12 of gestation, and the animals were killed on day 18 of gestation (Larsson and Boström, 1965). Untreated animals were used as controls. The incidence of resorption was 18.1 and 41.3% in A/Jax mice dosed on days 9 and 12, respectively; the incidence in controls was 10.6%. The incidence of resorption in CBA mice dosed on days 9 and 12 of gestation, 5.9 and 4.4% respectively, was less than that observed in control animals (9.6%). The incidence of vessel anomalies in animals dosed on day 12 of gestation was 11.9 and 0% for A/Jax and CBA mice, respectively; no vessel anomalies were seen in any of the controls.

In animals dosed on day 9 of gestation, the incidence of rib anomalies was 52.2 and 16.7% for A/Jax and CBA mice, respectively, as compared to 1.4 and 0% in controls, respectively. The incidence of vertebral anomalies was 33.3 and 4.0% in A/Jax and CBA mice, respectively, as compared to 1.9 and 0% in the respective controls.

Groups of five to eight gravid A/Jax and CBA mice were given a single i.m. dose of Sodium Salicylate, 10 mg/20 g body weight in 0.1 ml distilled water, on either day 9, 11, 13, 15, or 17 of gestation (Larsson and Eriksson, 1966). Animals were mated within and across strains. The animals were killed on day 18 of gestation.

Seven A/Jax mice, five of which were mated to CBA males, delivered prior to being killed on day 18; all seven had been given Sodium Salicylate on day 17 of gestation. In A/Jax females, the incidence of resorption generally increased the later Sodium Salicylate was administered. In A/Jax females mated with A/Jax males, the incidence of resorption was 19, 40, 67, 74, and 73% with injection on days 9, 11, 13, 15, and 17, respectively. In A/Jax females mated with CBA males, the incidence was 0, 14, 15, 41, and 25%, respectively. The incidence of resorption was much less in CBA mice. In CBA females mated with CBA males, the incidence of resorption was 8, 3, 7, 9, and 13% with injection on days 9, 11, 13, 15, and 17, respectively, and in CBA females mated with A/Jax males, the incidence was 0, 9,

7, 5, and 8%, respectively.

The following percent of offspring from dams dosed on the following days had vessel anomalies: day 9 - CBA females x A/Jax males - 2%; day 13 - A/Jax females x A/Jax males - 6% and A/Jax females x CBA males - 6%; day 15 - A/Jax females x A/Jax males - 58% and A/Jax females x CBA males - 41%; day 17 - CBA females x CBA males - 3%, A/Jax females x CBA males - 3%, and CBA females x A/Jax males - 8%.

Skeletal malformations were observed primarily in neonates of dams dosed on day 9 of gestation. Rib anomalies were observed in 49, 53, 47, and 24% of the neonates from A/Jax x A/Jax, CBA x CBA, A/Jax x CBA, and CBA x A/Jax animals that were dosed on day 9 of gestation, respectively, and vertebral anomalies were observed in 35, 12, 23, and 2% of these neonates, respectively. Three percent of the neonates from A/Jax x A/Jax animals dosed on day 11 had rib anomalies and 3% from CBA x CBA animals dosed on day 13 had rib as well as vertebral anomalies. No other neonates had skeletal anomalies. Encephaly and/or gastroschisis were observed in six neonates from CBA x A/Jax animals after dosing on days 9-15 of gestation, and exencephaly was observed in one neonate from a CBA x CBA animal. Cleft lip was "occasionally observed."

A group of 10 gravid A/Jax mice were given a single i.m. injection of 100 mg/ml Sodium Salicylate at a dose of 0.1 ml/20 g body wt on day 17 of gestation (Eriksson and Larsson, 1968). Five of the animals delivered on day 17 of gestation, two delivered on day 18, and three delivered on day 19. In the untreated control group three, six, and one gravid animal delivered on days 18, 19, and 20 of gestation, respectively, and in the saline-treated control group, three, three, and four gravid animals delivered on days 18, 19, and 20 of gestation, respectively.

Groups of 10-36 gravid A/Jax and CBA mice were given a single i.m. dose of 10 mg/20 g body wt Sodium Salicylate in 0.1 ml of distilled water on day 16, 17, or 18 of gestation; the animals dosed on day 16 or 18 were killed 8 or 24 h after dosing and the animals dosed on day 17 were killed 2, 4, 8, 12, or 24 h after dosing (Eriksson, 1969). Of the animals dosed on day 17, one CBA mouse that was to be killed after 8 h and two A/Jax and three CBA mice that were to be killed after 24 h delivered. Of the animals dosed on day 18, all seven A/Jax and all five CBA mice scheduled to be killed after 24 h delivered.

A higher percentage of fetal mortality was observed with A/Jax mice. In this strain, fetal mortality on day 16 of gestation was 46 and 43% after 8 and 24 h, respectively, and on day 17 was 0, 0, 19, 54, and 39% after 2, 4, 8, 12, and 24 h, respectively. In the CBA groups, fetal mortality on day 16 of gestation was 3 and 7% after 8 and 24 h, respectively, and on day 17 was 0, 5, 24 and 13% after 6, 8, 12, and 12 h, respectively. No fetal mortality was observed 8 h after dosing on day 18.

In A/Jax mice, the incidence of superficial hemorrhage along the spine on day 16 of gestation was 42 and 56% in viable fetuses 8 and 24 h after dosing, respectively, and on day 17 was 3, 35, 21, 52, and 20% in viable fetuses 2, 4, 8, 12, and 24 h after dosing, respectively. In the CBA groups, the incidence of superficial hemorrhage on day 16 of gestation was 49 and 21% in viable fetuses after 8 and 24 h, respectively, and on day 17 was 33, 56, 36 and 7% in viable fetuses after 6, 8, 12, and 12 h, respectively. No superficial hemorrhages were observed in viable fetuses 8 h after dosing on day 18. Superficial hemorrhage was observed in all dead animals that were examined. In A/Jax mice, the incidence of hepatic hemorrhage on day 16 of gestation was 19 and 26% in viable fetuses 8 and 24 h after dosing, respectively, on day 17 was 3, 3, 16, 30, and 20% in viable fetuses 2, 4, 8, 12, and 24 h after dosing, respectively, and on day 18 was 2% in viable fetuses after 8 h. In the CBA groups, the incidence of hepatic hemorrhage on day 16 of gestation was 11 and 0% in viable fetuses after 8 and 24 h, respectively, on day 17 was 3, 6, 0, and 0% in viable fetuses after 6, 8, 12, and 12 h, respectively, and on day 18 was 0% in viable fetuses after 8 h. No hepatic hemorrhages were observed in viable fetuses 8 h after dosing on day 18. All dead fetuses except three had hepatic hemorrhage.

Five CFE rats were given a single s.c. dose of 500 mg/kg Sodium Salicylate in 0.9% saline on day 8 of gestation and two rats were given daily s.c. doses of 100 mg/kg Sodium Salicylate on days 7-11 of gestation; the animals were killed on day 15 or 19 (Lansdown et al., 1970). Controls were given vehicle only. A single dose of 500 mg/kg resulted in 40% maternal toxicity. With this dose, the incidence of resorptions and dead

fetuses was 3% and the incidence of malformations was 6%. None of the animals dosed over 5 days died. With daily dosing, the incidence of resorptions and dead fetuses was 40% and the incidence of malformations was 10%. Aberrations in skeletal preosseous cartilage, particularly the cartilage matrix, were observed. The authors concluded that their findings suggested an inhibition of mucopolysaccharide synthesis during skeletal development.

Groups of 10 gravid A/Jax mice were given a single i.m. injection of 3, 10, or 15 mg Sodium Salicylate/20 g body wt in 0.1 ml distilled water on day 17 of gestation and the animals were killed on day 18 of gestation (Eriksson, 1970). Four animals of the 15 mg group died within 24 h of dosing, and four animals of this group delivered prior to being killed. Fetal mortality was 4, 70, and 100% in the 3, 10, and 15 mg groups, respectively. In the 10 mg group, the incidence of superficial, hepatic, and gastric hemorrhage in living fetuses was 39, 13, and 22%, respectively. No hemorrhages were observed in the 3 mg or control groups.

Groups of 10-20 gravid A/Jax mice were dosed with 10 mg Sodium Salicylate/20 g body wt as a single i.m. injection on day 15, 16, or 17 of gestation (Groups 1, 2, and 3, respectively) or as multiple i.m. injections on days 15, 16, and 17 of gestation (Group 4), while another group was dosed with 3 mg/20 g on days 15 and 16 and 10 mg/20 g on day 17 of gestation (Group 5) (Eriksson, 1970). (Ten of the 20 animals of Group 3 were from the study described above.) One animal of Group 2, two of Group 3, and one of Group 4 delivered before being killed. The incidences of fetal mortality, hemorrhages in viable fetuses, and vessel anomalies in viable fetuses are summarized in Table 10.

Five CFE rats were given a single s.c. dose of 500 mg/kg Sodium Salicylate in 0.9% saline on day 8 of gestation and two rats were given daily s.c. doses of 100 mg/kg Sodium Salicylate on days 7-11 of gestation; the animals were killed on day 15 or 19 (Lansdown et al., 1970). Controls were given vehicle only. A single dose of 500 mg/kg resulted in 40% maternal toxicity. With this dose, the incidence of resorptions and dead fetuses was 3% and the incidence of malformations was 6%. None of the animals dosed over 5 days died. With daily dosing, the incidence of resorptions and dead fetuses was 40% and the incidence of malformations was 10%. Aberrations in skeletal preosseous cartilage, particularly the cartilage matrix, were observed. Findings seem to suggest "that mucopolysaccharide synthesis had been inhibited during skeletal development"

Gravid Sprague-Dawley rats were given a s.c. injection of 50 or 100 mg/kg Sodium Salicylate 18 h prior to being killed on day 22 of gestation and gravid Havana rabbits were dosed s.c. with 50 mg/kg Sodium Salicylate 18 h prior to being killed on day 30 of gestation (Sharpe et al., 1975). Neonatal rats were whole-body frozen immediately or at 15, 30, or 60 min following delivery, and neonatal rabbits were frozen immediately upon delivery. In the rats, contraction of the intrauterine ductus was significant in neonates from both dose groups at 0, 15, and 30 min and from the 100 mg/kg dose group at 60 min as compared to controls. In test neonatal rabbits, ductal contraction was observed and ductal diameter was one-fifth that of controls.

Groups of 19-20 gravid Lakeview outbred (Lak: LVC) golden hamsters were given a single s.c. injection of Sodium Salicylate on day 8 of gestation, and the animals were killed on day 12 of gestation (Geber, 1977). The minimal effective teratogenic dose was 89 mg/kg Sodium Salicylate, which induced 2.8% congenital malformations. Doses of 37 and 45 mg/kg did not produce any congenital malformations.

Groups of six to eight gravid ferrets were given a single s.c. injection of 125, 250, or 400 mg/kg Sodium Salicylate on day 13 or 18 of gestation, and all animals were killed on day 35 of gestation (Gulamhusein et al., 1980). Control animals were dosed s.c. with 0.9% saline. No maternal toxicity was observed. Mean fetal weight was significantly decreased in all test groups compared to controls. The resorption rates were 6, 33, 31, and 91% in the control, 125, 250, and 400 mg/kg dose groups dosed on day 13. Resorption rates of 6, -43, 37, and 66% in the control, 125, 250, and 400 mg/kg group dosed on day 18.

The incidence of external and internal abnormalities in surviving fetuses was 2, 11, 0, and 86% in the control, 125, 250, and 400 mg/kg dose groups dosed on day. The incidence of external and internal abnormalities in surviving fetuses of animals dosed on day 18 was 2, 7, 33, and 96% in the control, 125, 250, and 400 mg/kg dose groups.

Table 10. Incidence of Fetal Mortality, Hemorrhage, and Vessel Anomalies in Mice Treated with Sodium Salicylate (Eriksson, 1970)

i.m. Dosing	#Litters	Fetal Mortality (%)	Superficial Hemorrhage (%)	Hepatic Hemorrhage (%)	Gastric Hemorrhage (%)	Vessel Anomalies (%)
10 mg/20 g on gestation day 15	10	39	2	0	0	27
10 mg/20 g on gestation day 16	10	55	42	0	0	0
10 mg/20 g on gestation day 17	20	61	27	12	31	0
10 mg/20 g on gestation days 15, 16, and 17	20	47	4	5	9	33
3 mg/20 g on gestation days 15 and 16; and 10 mg/20 g on gestation day 17	20	21	3	12	36	0

The results in ferrets were compared to those in Wistar rats following a single s.c. dose of 400 mg/kg Sodium Salicylate given on day 8.5 or 11.5 of gestation; groups of 5-10 gravid animals were used. The rats were killed on day 20.5 of gestation. Mean fetal body weights were significantly reduced in both test groups. The resorption rates were 23 and 9% and the incidence of external and internal abnormalities in surviving fetuses was 19 and 11% with dosing on days 8.5 and 11.5, respectively. Sodium Salicylate was more embryotoxic in ferrets than in rats.

Gravid golden hamsters were given a single i.p. dose of 1100 mg/kg Sodium Salicylate on day 8 and killed on day 15 of gestation (Beyer and Geber, 1984). Control animals were dosed with saline. A trend toward increased mean lateral ventricle size was observed in test animals as compared to controls.

Groups of gravid Sprague-Dawley rats were given i.v. injections of Sodium Salicylate either as single injections or as a constant infusion (Gabrielsson et al., 1985). Groups of three to nine animals were given single injections of 15, 50, 100, 200, or 500 mg/kg Sodium Salicylate on day 6 of gestation, and blood samples were taken at various intervals from 1 min to 30 h after dosing. Groups of 11 animals were given a single daily i.v. dose of 75 or 150 mg/kg Sodium Salicylate on days 6-13 of gestation, and five animals were given single daily i.v. doses of 150 mg/kg on days 13-19 of gestation. Fourteen or 12 animals were dosed via constant infusion with 1 or 2 mg/h (corresponding to 75 or 150 mg/kg/day) Sodium Salicylate, respectively, on days 6-13 of gestation, and blood samples were taken on the days of dosing. Eleven animals were constantly infused with 150 mg/kg/day Sodium Salicylate on days 13-19 of gestation. A control group of 10 animals was infused with saline on days 6-13 of gestation. The animals were killed on day 19 of gestation.

In the animals given a single i.v. dose of Sodium Salicylate on day 6 of gestation, fetal body weights were decreased in the 50-500 mg/kg test groups when compared to the low dose group. Compared to the controls, a significant decrease in fetal weight was observed in animals given a continuous infusion of 150 mg/kg and in animals given daily doses of 150 mg/kg on days 6-13 of gestation.

The incidence of resorbed and dead fetuses was 0, 4, 11.6, 15, and 47.6% in the 15, 50, 100, 200, and 500 mg/kg dose groups, respectively. The incidence was 42 and 81% in the animals dosed daily with 75 and 150 mg/kg/day, respectively, on days 6-13 of gestation and 0% in the animals dosed with 150 mg/kg/day on days 13-19 of gestation.

The incidence of resorbed and dead fetuses in animals given continuous infusions of Sodium Salicylate was 4 and 73% in the animals dosed with 75 and 150 mg/kg/day, respectively, on days

6-13 of gestation and 6% in the animals dosed with 150 mg/kg/day on days 13-19 of gestation. The incidence in controls was 3%.

Groups of gravid New Zealand White rabbits were given a continuous i.v. infusion of Sodium Salicylate on days 22-29 of gestation (Lukas et al., 1987). (The animals were placed in the infusion harnesses on day 19 for purposes of acclimation.) Four animals were infused with 60 mg/ml Sodium Salicylate in sterile water at a rate of 1.2 ml/h, with a target maternal plasma salicylate concentration of 10-15 mg/dl, and three animals were infused with 80-120 mg/dl at the same rate, with a target maternal plasma salicylate concentration of >20 mg/dl. A control group of three animals were infused with normal saline at the rate of 1.2 ml/h. Daily maternal blood samples were drawn to monitor maternal plasma concentrations. The animals were killed on day 29 of gestation.

Maternal weight decreased in the test and control groups. Average litter size was not affected by Sodium Salicylate administration. The only fetal mortality was observed in the high dose group, in which there was three fetal deaths; this was not significant. The fetal/maternal Sodium Salicylate concentration ratios were 1.02 and 0.86 in the low and high dose groups, respectively. Mean fetal weights, fetal crown-rump length, the ratio of fetal weight per cm crown-rump length, placental weight, and absolute and relative liver weights were significantly decreased in both test groups as compared to controls. The relative placental weight was significantly increased in the high dose group. Absolute brain weight was significantly decreased in the high dose group and the relative brain weight was significantly increased in both test groups compared to controls.

The effect of a single i.p. injection of Sodium Salicylate on fetal joint development was examined using gravid BALB/c mice (Erdoğan et al., 1996). A dose of 500 mg/kg was administered on day 10 of gestation. Dosing with Sodium Salicylate resulted in lost articulatio cubiti joint spaces and surfaces, fusion between the humerus-radius and ulna, disappearance of some carpo-metacarpal joint spaces, absence of the fifth phalanx, overgrowth in tibia condyles, and occasional fusions in tarsometatarsal joints and between metatarsal bones with an absence of phalanges.

Table 11summarizes the *in vivo* reproductive and developmental toxicity studies described in this section.

RISK ASSESSMENT

The possible teratogenic effects of aspirin were examined by reviewing retrospective studies of aspirin consumption during pregnancy (Corby, 1978). It stated "that, although direct conclusive evidence of adverse effects in humans is lacking, a potential hazard does exist and thus "the indiscriminate use of aspirin during pregnancy is contraindicated."

A risk assessment was developed addressing the safety of facial cosmetic products containing ≤2% Salicylic Acid using oral studies on ASA (aspirin) as well as the conclusions of the Teratogen Information Service (TERIS), a computerized database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women (Procter and Gamble Company, 1999a). The assessment stated that exposure to cosmetic products intended for use in the face/neck area (daily use) is expected to be in the range of 1.1 g/day, with 95th percentile users applying 1.4 g/day. For a 58 kg female, the average product use would then be approximately 19 mg product/-kg/day, with 95th percentile users applying 24 mg product/kg/day. If the product contained 2% Salicylic Acid, this would correspond to topical applied doses of 0.38 and 0.48 mg Salicylic Acid/ kg/day, respectively. The assessment stated that oral ingestion of "baby aspirin" (containing 81 mg ASA/62 mg Salicylic Acid) would yield an exposure of 1.05 mg/kg for a 58 kg female. Therefore, systemic salicylate exposure from a facial cosmetic product containing 2% Salicylic Acid is expected to be in range of ~20% of that following ingestion of a single baby aspirin, "a salicylate dose widely recognized as carrying no maternal or fetal risk." Additionally, the risk assessment stated that "because availability of [Salicylic Acid] from cosmetic products is low, concomitant use of such products with other topical [Salicylic Acid] containing products would not substantially increase the risk of developmental or reproductive toxicity."

Table 11. Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Dermal Exposute to:				
Methyl Salicylate				
12 rats/gp	1, 3, or 6 g/kg of a petroleum based grease using 3% Methyl Salicylate	Dermal applications were made on gestation days (GDs) 6-15; positive controls were dosed dermally with 2 and 1 g/kg Methyl Salicylate on GDs 6-9 and 10-15; dose was changed due to maternal toxicity (tox.)	No maternal toxicity and no changes in reproductive parameters or malformations were seen; positive controls had 100% incidence of total resorptions	Infurna et al., 1990
LVG hamsters	Not specified	Methyl Salicylate was applied to the back of each animal	Application at 7 d 9 h caused failure in neural tube closure in 75% of embryos recovered at 9 d 0 h	Overman, 1979
LVG hamsters	350 or 525 mg/100 g	Methyl Salicylate was applied to the back of each animal at 7 d 9 h, and the skin was washed 2 h after dosing; fetuses were recovered on d 9 of gestation	Neural tube defects were seen in 6% and 53% of the low and high dose litters, respectively	Overman and White, 1983
Oral Exposure to:				
Salicylic Acid				
20 Wistar rats/group	0.06, 0.1, 0.2, or 0.4% in feed	Animals were fed test diets on GDs 8-14; 15 animals/gp were killed on GD 20; 5 animals/group delivered	Maternal mortality was 0%; neonatal mortality was 71% in the 0.4% group; significant reproductive effects were seen in the 0.4% group; skeletal anomalies were seen in the 0.2% group; only one dam gave birth to live neonates in the 0.4% group and skeletal anomalies were seen in 0.2% neonates	Tanaka et al., 1973a
20 Wistar rats/group	75, 150, or 300 mg/kg	Animals were dosed orally once daily on GDs 8-14; 15 animals/gp were killed on GD 20; 5 animals/gp delivered	3 dams of the 300 mg/kg gp died; fetal mortality was 26 and 100% in the 150 and 300 mg/kg gps; significant reproductive effects were seen in 150 mg/kg fetuses and neonates	Tanaka et al., 1973b
10 Sprague-Dawley (SD) rats/group	10 mg/kg	Animals were dosed twice daily on GD 20 and 21	The mean gestation period was increased	Waltman et al., 1973
Sodium Salicylate				
NZW rabbits	100 mg/kg	Animals were dosed on GDs 4-7 and killed on GD 8 or 28	The preimplantation ratio and avg litter size were not affected; teratogenic effects were not induced	Fabro et al., 1984
21 albino rats/group	200 mg/kg (2 groups)	Animals were dosed on GDs 6-15 and killed on GD 20	Significant increase in resorptions and decrease in viable fetuses seen in 1 group ;in external and internal abnormalities sig. incr. in 2nd group; and skeletal anomalies in both groups	Keplinger et al., 1974
17-19 SD rats/group	30, 90, or 180 mg/kg	Animals dosed on GDs 6-15 and killed on GD 21	Teratogenicity was 30% in the 180 mg/kg group, and marked embryotoxicity occurred; maternal toxicity was low; growth decreased in the 90 and 180 mg/kg grooups (dose-dependent).	Fritz and Giese, 1990

Table 11 (cont.). Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Sodium Salicylate (oral exposures continued)				
CD-1 mice SD rats	Mice: 1500 mg/kg Rats: 300 mg/kg	Animals were dosed on GD 7, 8, 9, 10, or 11; mice were killed on GD 18 and rats on GD 21	Mice: fetal mortality increased w/dosing on day 10; skeletal anomalies increased w/dosing on days 8 and 9; rats: skeletal anomalies increased w/dosing on day 8 and 10	Beyer and Chernoff, 1986
19 or 37 CD-1 mice	2000 and 2600 mg/kg	Animals were dosed on GD 8 and killed on GD 18	2000 mg/kg: 11% maternal mortality, 71% viable litters, 14% fetal mortality; 7% of fetuses w/malformations; 2600 mg/kg: 24% maternal mortality, 79% viable litters, 7% fetal mortality; 3% of fetuses w/malformations	Kavlock et al., 1985
2 CFE rats/group	500 or 100 mg/kg	Animals were given a single dose of 500 mg/kg on GD 8 and 100 mg/kg on GD 7-11 and killed on GD 15 or 19	500 mg/kg: 50% maternal toxicity; 53% resorptions and dead fetuses, 13% malformations; 100 mg/kg: 15% incidence of resorptions and dead fetuses	Lansdown et al., 1970
22 CD-1 mice	800 mg/kg	Animals were dosed on GDs 8-12 and allowed to deliver	Avg neonatal wt was decreased on postnatal days 1 and 3	Chernoff and Kavlock, 1982; 1983
30 ICR/SIM mice	1600 mg/kg	Animals were dosed on GDs 8-12 and allowed to deliver	Seven dams died; neonate survival and avg. no. viable neonates/litter on days 1 and 3 was significantly decreased and no. dead neonates/litter on day 1 was significantly increased.	Seidenberg et al., 1986
25 A/Jax mice	66.6 mg/ml	Animals were dosed on GD 17; 5 dams were killed 4 h and the remaining 20 were killed 24 h after dosing	One dam delivered between 5-24 h; fetal mortality was 47% and the incidence of superficial, hepatic, and gastric hemorrhage was 6, 1, and 2% in the animals killed at 24 h; fetal hepatic glycogen was significantly decreased	Eriksson, 1971
12-15 albino rats/group	25, 75, or 150 mg/kg	Animals were dosed on GD 15-20 and allowed to deliver; neonates were killed on day 42	Parturition was delayed in one and two dams of the 25 and 150 mg/kg gps; in the 150 mg/kg gp, neonatal mortality incr. in a dose-dependent manner	Fritz and Suter, 1985
	4.2, 12.5, or 25 mg/kg	Animals were dosed on GD 20-21 and allowed to deliver; neonates were killed on day 42	In the 12.5 and 25 mg/kg gps, neonatal mortality increased in a dose-dependent manner	
10 SD rats/group	10 mg/kg	Animals were dosed twice daily on GD 20 and 21 and allowed to deliver	The duration of and bleeding at parturition was increased; 13/121 neonates were born dead	Waltman et al., 1973
SD and Long-Evans rats	125 or 175 mg/kg	Animals were dosed on GD 8-10 and allowed to deliver; locomotor activity was tested using clean and homecage bedding	No malformations were seen; alterations in activity were seen (male neonates had more salicylate-related changes than females)	Buelke-Sam et al., 1984
Methyl Salicylate				
LVG hamsters	175 mg/100g	Animals were dosed at 7 d 9 h of gestation and killed on GD 9	72% of 35 litters had neural defects; Salicylate reached the fetus	Overman and White, 1983
24-27 SD rats/group	4000 or 6000 ppm	Animals were fed test diet w/calcium carbonate for 60 days prior to mating through weaning at day 20 or 21; procedure was then repeated	No abnormalities noted in offspring; neonate survival at weaning was greater in the test than the control groups	FDA, 1966

Table 11 (cont.). Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Methyl Salicylate (oral exposures continued)				
F_0: 25 mice/sex/group F_{1b}: 30 males/30 females/group	0.25 or 0.5% in feed	Animals were dosed for 30 days prior to mating; F_0 animals were mated twice F_{1a} animals maintained through weaning F_{1b} animals mated twice	(Results are only from females in each generation that mated twice) No gross abnormalities were observed w/any litter; all surviving neonates appeared normal; no reproductive abnormalities were seen	Abbott and Harrisson, no date
F_0: 25 Wistar rats/ sex/group F_{1b}: 30/sex//group	0.25 or 0.5% in feed	Same protocol as above, with the exception that the animals were dosed for 60 days prior to mating	No gross abnormalities were observed w/any litter; all surviving neonates appeared normal; mating performance and reproduction and viability indices were decreased. and # of deaths between birth and day 5 were increased in the 0.5% group; litter size was decreased in both test groups	Abbott and Harrisson, no date
F_0: 10 Osborne-Mendel rats/sex/group	500, 1500, 3000, or 5000 ppm in feed	F_0 animals mated after 100 days of dosing; F_{1a} animals were killed at weaning; 20 littermated F_{1b} animals were mated; procedure was repeated until generation 3	No gross abnormalities were observed; various reproductive effects were seen, especially in the 2nd generation	Collins et al., 1971
male and female CD-1 mice	25, 50, or 100 mg/kg	Reproductive assessment by continuous breeding; control and high dose F_1 offspring reproductive and fertility performance was evaluated due to lack of effect in F_0 mice	Reproductive and fertility parameters were generally not affected; also no significant effect on mating behavior, fertility rate, or reproductive performance was seen	Research Triangle Institute, 1984; Morrissey et al., 1989; Lamb et al., 1997a
20 CD-1 mice/sex/ gp	100, 250, or 500 mg/kg	Reproductive assessment by continuous breeding; crossover mating trial was performed to determine affected sex	Significnat decrease seen in the mean # litters, avg # of pups/litter, proportion of live pups, and mean live pup weights in the high dose group; fertility was poor in all gps, so the affected sex was not determined	Environmental Health Research Testing, Inc, 1984; Morrissey et al., 1989; Lamb et al., 1997b
CD rats	0.05 or 0.1 ml	Animals were dosed on GD 10 and 11 and either killed on GD 21 or allowed to deliver	The 0.1 ml group had decrreased body weight gain, fewer and smaller neonates, and more resorptions and malformed neonates; fetal kidney weight was decreased (GD 21) but was not different from control on postnatal day 6.	Woo and Hoar, 1972
Parenteral Exposures to:				
Salicylic Acid				
17 SD rats	380 mg/kg	Animals were given a divided dose s.c. on GD 9, and then injected w/mineral isotopes; the animals were killed in GD20	Marked maternal weight loss; mean fetal wt was significantly decreased; the resorption rate was 46.6%, and 5.3% of viable fetuses were malformed; urinary mineral excretion was not affected	Koshakji and Schulert, 1973
3-4 SD rats/group	300 or 380 mg/kg	Animals were given a divided dose s.c. on GD 16, and then injected w/mineral isotopes; the animals were killed after 6 or 24 h	The high dose caused hematuria (3 cases) a high rate of fetal mortality and superficial hemorrhage; maternal-fetal uptake of minerals was not affected	Koshakji and Schulert, 1973

Table 11 (cont.). Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Sodium Salicylate				
19-20 Lak:LVC golden hamsters/group	37, 45, or 89 mg/kg	Animals were dosed s.c. on GD 8 and killed on GD 12	The minimal effective teratogenic dose was 89 mg/kg (produced 2.8% congenital malformations)	Geber, 1977
5 CFE rats	500 mg/kg on GD 8 100 mg/kg daily on GD 7-11	s.c. dose	The single dose caused 40% maternal toxicity and a 3 and 6% incidence of resorptions and dead fetuses and malformations, respectively; daily dosing resulted in 40 and 10% incidence of resorptions and dead fetuses and malformations, respectively	Lansdown et al., 1970
43 Rats	60-180 mg	Animals were dosed s.c on GD 9, 10, or 11 and killed on GD 21	Six dams given >120 mg died (no other information as a function of dose given); 24 animals resorbed their fetuses; external abnormalities in 15/100 fetuses; 11 of the 85 fetuses that appeared normal had skeletal anomalies	Warkany and Takacs, 1959
9-42 SD rats/group	200-500 mg/kg	Animals were dosed s.c. on GD 10 and killed on GD 20	Significant numbers of fetal anomalies in the 400 and 500 mg/kg groups	Goldman and Yakovac, 1963
6-8 ferrets/group	125, 250,or 400 mg/kg	Animals were dosed s.c. on GD 13 or 18 and killed on GD 35	Mean fetal wt was significantly decreased in all groups; resorption rates were 33, 31, and 91% and 43, 37, and 66% for the 125, 250, and 400 mg/kg groups dosed on GD 13 and 18, respectively; incidence of abnormalities was 11 and 86% for the 125 and 400 mg/kg group dosed on GD 13 and 7, 33, and 96% for the 125, 250, and 400 mg/kg group dosed on GD 18	Gulamhusein et al., 1980
5-10 Wistar rats/group	400 mg/kg	Animals were dosed s.c. on GD 8.5 or 11.5 and killed on GD 20.5	Mean fetal weight was significantly decreased in both groups; resorption rates were 23 and 9%, and the incidence of abnormalities was 19 and 11% w/dosing on GD 8. and 11.5, respectively	Gulamhusein et al., 1980
SD rats	50 or 100 mg/kg	Animals were dosed s.c. 18 h prior to being killed on GD 22; fetuses were frozen immediately, or 15, 30, or 60 min after delivery	Contraction of the intrauterine ductus was significant in both groups at 0, 15, and 30 min and the high dose group at 60 min	Sharpe et al., 1975
Havana rabbits	50 mg/kg	Animals were dosed s.c. 18 h prior to be killed on GD 30; fetuses were frozen immediately	Ductal contraction was observed and ductal diameter was 1/5 control values	
1-5 rats/group	0.20-0.75 g/kg	Animals were given a single s.c. dose the last wk of pregnancy and killed after 2 days	Maternal mortality was 2/5 and 3/3 in the 0.5 and 0.75 mg/kg groups; all fetuses of surviving animals lived	Jackson, 1948
2-4 rabbits/group	0.5 or 1.0 g/kg	Same as above	Maternal mortality was 1/4 and 2/2 in the 0.5 and 1.0 groups; 19/23 fetuses of surviving animals lived	
A/Jax mice	10 mg	Animals dosed i.m. on one of GD 7-13 and killed on GD 18	A high incidence of external anomalies was seen w/dosing on GD 12 or 13 and of deformities of ribs and vertebrae was seen in all groups	Larsson et al., 1963

Table 11 (cont.). Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Sodium Salicylate (parenteral exposures continued)				
A/Jax mice	10 mg	Animals were dosed i.m. on GD 9 or 12 and killed on GD 18	Incidence of resorption: 18.1 and 43.3%, GD 9 and 12 ; vessel anomalies: 11.9%, GD 12; rib anomalies: 52.2%, GD9: vertebral anomalies: 33.3 %, GD12	Larsson and Boström, 1965
CBA mice			Incidence of resorption: 5.9 and 4.4%, GD 9 and 12 ; vessel anomalies: 0%, GD12; rib anomalies:16.7% , GD9; vertebral anomalies: 4.0%, GD12	
5-8 A/Jax and CBA mice/group	10 mg/20 g	Animals, which were mated within and across strains, were dosed i.m. on GD 9, 11, 13, 15, or 17	A/Jax females x A/Jax males: resorption: 19-73%; vessel anomalies: 6-58%; rib anomalies (GD9): 49%; vertebral anomalies (GD9): 35% A/Jax females x CBA males: incidence of resorption: 0-41%; vessel anomalies: 3-41%; rib anomalies (GD9): 47%; vertebral anomalies (GD9): 23% CBA females x CBA males: incidence of resorption: 3-13%; vessel anomalies: 3%; rib anomalies (GD9): 53%; vertebral anomalies (GD9): 12% CBA females x A/Jax males: incidence of resorption: 0-9%; vessel anomalies: 2-8%; rib anomalies (GD9): 24%; vertebral anomalies (GD9): 2%	Larsson and Eriksson, 1966
10 A/Jax mice	10 mg/20 g	Animals were dosed i.m. on GD 17	5, 2, and 3 animals delivered on GD 17, 18, and 19	Eriksson and Larsson, 1968
10-36 A/Jax and CBA mice/group	10 mg/20 g	Animals were dosed i.m. on GD 16 or 18 and killed after 8 or 24 h or dosed on GD 17 and killed after 2, 4, 8, 12, or 24 h	Many animals delivered prematurely; fetal mortality was greater w/A/Jax mice; superficial and hepatic hemorrhage was seen in both strains	Eriksson, 1969
10 A/Jax mice/group	3, 10, or 15 mg/20 g	Animals were dosed i.m. on GD 17 and killed on GD 18	In the 15 mg group, 4 animals died within 24 h and 4 delivered prematurely; fetal mortality was 4, 70, and 100 in the 3, 10, and 15 mg groups; incidence of superficial, hepatic, and gastric was hemorrhage was 39, 13, and 22% in the 10 mg group	Eriksson, 1970
10-20 A/Jax mice/group	10 or 3 mg/20 g	Animals were dosed i.m. w/10 mg on GD 15, 16, or 17 or on GDs 15-17 or w/3 mg on GD 15 and 16 and 10 mg on GD 17	Some animals delivered prematurely; fetal mortality was 21-61%, superficial, hepatic, and gastric hemorrhage was 2-42, 0-12, and 0-36%, and vessel anomaly was 0-33%	Eriksson, 1970

Table 11 (cont.). Reproductive and Developmental Toxicity Studies

Animals	Dose	Methods	Results	Reference
Sodium Salicylate (parenteral exposures continued)				
3-14 SD rats/group	15-500 mg/kg (see methods)	Animals were dosed i.v. as follows: single dose of 15, 50, 100, 200, or 500 mg/kg on GD 6; daily doses of 75 or 150 mg/kg on GDs 6-13 ; daily dose of 150 mg/kg on GD 13-19; constant infusion of 75 or 150 mg/kg/day on GD 6-13 ; and constant infusion of 150 mg/kg/day on GD 13-19; the animals were killed on GD 19	Fetal body weights were decreased in the groups given a single dose of 50-500 mg/kg, and daily doses of 150 mg/kg or continuous infusion of 150 mg/kg on GD 6-13 Incidence of resorbed and dead fetuses for different dose regimes was: single dose:15mg - 0%; 50 mg - 4%; 100 mg - 11.6%; 200 mg - 15%; 500 mg - 47.6% daily dose GD 6-13: 75 mg - 42%; 150 mg - 81% daily dose GD 13-19: 150 mg - 0% infusion GD 6-13: 75 mg - 4%; 150 mg - 73% infusion GD 13-19: 150 mg - 6%	Gabrielsson et al., 1985
3-4 NZW rabbits/group	60 mg/ml or 80-120 mg/dl	Animals were given cont. infusions on GD 22-29 and killed on GD 29	Mean fetal wt, fetal crown-rump length, ratio of fetal wt/cm crown-rump length, placental wt, and absolute and relative liver wts were sig decr. in both gps	Lukas et al., 1987
golden hamsters	1100 mg/kg	Animals were dosed i.p. on GD 8 and killed on GD 15	A trend toward incr. mean lateral ventricle size was observed	Beyer and Geber, 1984
5 CFE rats/group	100 or 500 mg/kg	Animals were dosed i.p. daily w/100 mg/kg on GD 7-11 or once w/500 mg/kg on GD 8; the animals were killed on GD 15 or 19	The incidence of resorptions and dead fetuses and of malformations was 36 and 8% w/the multiple dose and 81 and 16% w/the single dose	Lansdown et al., 1970
balb/c mice	500 mg/kg	Animals were dosed i.p. on GD 10	Effects on fetal joint development were seen	Erdoğan et al., 1996
Methyl Salicylate				
116 Rats	0.1-0.5 cc	Animals were dosed s.c. on GD 9, 10, or 11 and killed on GD 21	26/69 dams died; 47 resorbed their fetuses; external abnormalities in 45/298 fetuses; 75 of the 253 fetuses that appeared normal had skeletal anomalies (no information given as a function of dose)	Warkany and Takacs, 1959
5 CD rats	200 or 400 mg/kg	Animals were dosed i.p. on GD 8-9 and killed on GD 20	Embryotoxicity was seen at 400 mg/kg; fetal mortality was 2 and 50% in the 200 and 400 mg/kg groups; fetal body weight index was significantly decreased in the 400 mg/kg group; some developmental anomalies were seen in both groups, and dose-related decreases in organ weights were observed	Kavlock et al., 1982

Animals	Dose	Methods	Results	Reference
Methyl Salicylate (parenteral exposures continued)				
5-16 SD rats	250-450 mg/kg	nimals were dosed i.p. w/250-450, 200-300, 300-375, or 200-300 mg/kg on GD 11, 10-11,11-12, or 11-13 and killed on GD 20	Maternal tox. was observed; fetal weight was significantly decreased (dose-dependent); malformations were observed in fetuses of groups dosed w/≥350 mg/kg on GD 11 and ≥300 mg/kg on >1 day; incidence of resorptions was significant in the 400 mg/kg gp dosed on GD 11; kidney development was affected	Daston et al., 1988
SD rats	200, 250, or 300 mg/kg	Animals were dosed i.p. on GD 10-13	A high incidence of maternal mortality was seen in the 300 mg/kg group; neonatal mortality was increased in the 250 and 300 mg/kg groups on days 1-2; no external abnormalities were seen in surviving neonates; some effect on urine-concentrating ability was seen in young neonates	Daston et al., 1988

MODULATION OF SALICYLATE-INDUCED REPRODUCTIVE EFFECTS

Oral Studies

Salicylic Acid

Gravid NMRI mice were dosed orally with 500 or 1000 mg/kg Salicylic Acid, 500 mg/kg Salicylic Acid plus 500 mg pyridyl-3-methanol, or 1000 or 2000 mg/kg of an ester of Salicylic Acid plus pyridyl-3-methanol (the combination was referred to as S-2063) in 1% carboxylmethyl cellulose at a volume of 0.2 ml/20 g (Cekanova et al., 1974). Groups of 11-14 animals were dosed on day 9 and groups of 5-13 animals were dosed on day 17 of gestation. Controls were dosed with vehicle. The animals were weighed on day 0 and days 9-18, and killed on day 18 of gestation.

Four of the animals dosed with 1000 mg/kg Salicylic Acid and three of those dosed with 2000 mg/kg S-2063 mixture on day 9 of gestation, and three of the animals dosed with 1000 mg/kg Salicylic Acid and three dosed with 2000 mg/kg S-2063 mixture on day 17 of gestation died after dosing. One female of the 500 mg/kg Salicylic Acid and one of the 1000 mg/kg S-2063 mixture dose group delivered prematurely.

In the animals dosed on day 9, the incidence of resorbed fetuses prior to day 17 was 16.0, 19.5, 19.5, 12.6, and 25.3% for the 500 and 1000 mg/kg Salicylic Acid groups, the Salicylic Acid and pyridyl-3-methanol group, and the 1000 and 2000 mg/kg S-2063 mixture groups, respectively; the incidence of resorbed fetuses after day 17 was <1%. In the animals dosed on day 17, the incidence of resorbed fetuses prior to day 17 was 11.5, 17.2, 9.3, 11.0, and 16.7% for the 500 and 1000 mg/kg Salicylic Acid groups, the S-2063 mixture (again, this mixture is Salicylic Acid and pyridyl-3-methanol) group, and the 1000 and 2000 mg/kg S-2063 groups, respectively. The respective incidences of resorbed fetuses after day 17 were 4.1, 48.3, 2.7, 0.7, and 8.3%; the resorptions occurred in one, two, or three litters. In the animals dosed on day 9, the incidence of malformations was 4.5, 26.7, 8.9, 3.2, and 23.8% for the 500 and 1000 mg/kg Salicylic Acid groups, the Salicylic Acid and pyridyl-3-methanol group, and the 1000 and 2000 mg/kg groups, respectively.

Methyl Salicylate

In a study described previously, Collins et al. (1971) also examined the effect of the addition of calcium carbonate to Methyl Salicylate-supplemented diet. Groups of F_{2b} rats were given 1500 ppm calcium carbonate (600 ppm available as calcium) in addition to 500, 1500, 3000, or 5000 ppm Methyl Salicylate. The animals were mated, and the first and second litters were examined. The addition of calcium carbonate did

not markedly alter the effects obtained with Methyl Salicylate only.

Sodium Salicylate

The effect of dietary zinc and genetic strain on salicylate-induced teratogenesis was determined in the rat (Hackman and Hurley, 1984). Groups of three to eight gravid Sprague-Dawley and four to 10 Wistar rats were fed a zinc-deficient diet containing 0.4 µg zinc/g diet (designated as 0 µg/g), purified diets in which the zinc concentration was adjusted to 4.5, 9, 100, or 1000 µg zinc/g diet, or stock diet (which contained 40 µg zinc/g diet). On day 9 of gestation, the animals were dosed orally with 250, 500, or 750 mg/kg Sodium Salicylate or 0.9% sodium chloride. All animals were killed on day 21 of gestation.

The number of total viable fetuses, and the pooled proportions of resorptions (Res/T) and resorptions + malformations per total sites (Res+ Mal/T) and of malformations per total viable fetuses (Mal/Viable) are summarized in Table 12a for the Sprague-Dawley strain and 12b for the Wistar strain. Data for Wistar rats on stock diet were not reported. Wistar rats appeared more sensitive than Sprague-Dawley rats to Sodium Salicylate-induced teratogenesis. The frequency of resorption, malformed fetuses, and total abnormal sites generally decreased with increased zinc concentrations.

Groups of female Sprague-Dawley rats were fed basal diet containing 0.15 ppm sodium selenite or a diet containing 4.5 ppm sodium selenite for 8 wks (Bergman et al., 1990). After 8 wks, the animals were mated and maintained on their respective diets. Groups of 10-18 gravid animals, which were fed a basal or selenite-supplemented diet, were dosed orally with either 250 mg/kg Sodium Salicylate in distilled water or physiological saline once daily on days 6-13 of gestation. All animals were killed on day gestation.

Selenite did not have a reproductive or teratogenic effect in animals given physiological saline. The number of surviving fetuses (42.6% of implants and 4.7 fetuses per litter were resorbed or dead) and fetal weight (0.99 g) was decreased in animals fed the basal diet and dosed with Sodium Salicylate; malformations were observed in 50.4% of the fetuses, a total of 83 malformations were observed in 57 of 113 fetuses.

In animals fed the selenite-supplemented diet and dosed with Sodium Salicylate, an increase in fetal survival was observed compared to the test group fed a basal diet (34.4% of implants and 4.0 fetuses per litter were resorbed or dead), but the incidence of fetal malformations was significantly increased compared to test animals given the basal diet; 66.0% of the fetuses were malformed, and a total of 152 malformations were observed in 95 of 144 fetuses. Selenite supplementation did not affect oral Sodium Salicylate embryotoxicity.

The interaction between Sodium Salicylate and murine cytomegalovirus (MCMV) was examined using gravid CD-1 mice (Francis et al., 1990). Groups of six to 15 gravid animals were dosed i.p. with 1×10^4 or 5×10^4 plaque-forming units MCMV on day 8 of gestation and orally with 500 or 750 mg/kg Sodium Salicylate on days 9 and 10 of gestation. Controls were given vehicle, MCMV, or Sodium Salicylate only. The animals were killed on day 18 of gestation. No synergistic effects of MCMV and Sodium Salicylate were observed. Sodium Salicylate alone was not fetotoxic.

Parenteral Studies

Sodium Salicylate

A group of 20 gravid A/Jax mice was given i.p. injections of 1.5 mg pentobarbital/20 g body wt on days 15 and 16 of gestation and an i.m. injection of 10 mg Sodium Salicylate/20 g body wt on day 17 of gestation, while a control group was given pentobarbital only (Eriksson, 1970). Fetal mortality was 31 and 5% in the pentobarbital/Sodium Salicylate and pentobarbital only groups, respectively. Compared to results of a previously-described study, pentobarbital pretreatment decreased the damaging effects of Sodium Salicylate (reported 61% mortality). In viable fetuses from animals given pentobarbital and salicylate, the incidence of superficial, hepatic, and gastric hemorrhage was 26, 9, and 37%, respectively; in the salicylate-only group, the respective incidences were 1, 0, and 1%. The effect of salicylate and pentobarbital on maternal hepatic microsomal hydroxylating enzymes was examined. Salicylate did not affect these enzymes.

Table 12a. Effect of Zinc on Sodium Salicylate-induced Teratogenesis in Sprague-dawley Rats (Hackman and Hurley, 1984)

Zinc (µg/g)	Salicylate (mg/kg)	# Litters	Total Viable Fetuses	Res/T (%)	Res+Mal/T (%)	Mal/Viable (%)
Zn defficient (0.4)	0	6	41	30	84	78
Zn defficient (0.4)	250	5	32	37	100	100
Zn defficient (0.4)	500	7	43	41	93	88
Zn defficient (0.4)	750	6	2	96	98	50
4.5	0	7	57	16	19	3
4.5	250	6	43	23	38	14
4.5	500	7	49	31	52	3
4.5	750	6	26	51	66	3
9	0	7	63	10	10	0
9	250	4	34	8	8	0
9	500	7	42	37	43	9
9	750	4	10	73	73	0
100	0	7	64	8	8	0
100	250	5	47	0	2	0
100	500	6	38	35	45	15
100	750	5	41	49	52	4
1000	0	8	70	12	13	1
1000	250	5	51	3	0	0
1000	500	7	52	27	31	5
1000	750	6	24	63	73	29
Stock (40)	0	4	43	0	0	0
Stock (40)	250	3	28	12	12	0
Stock (40)	500	5	49	9	12	4
Stock (40)	750	6	38	39	44	7

Groups of five to 14 gravid CBA mice were dosed i.m. with 500 mg/kg Sodium Salicylate or 500 mg/kg Sodium Salicylate and 2.5 or 25 mg/kg $PGF_{2\alpha}$ at various times on day 9 of gestation, and the animals were killed on day 16 (Marsk, 1980). Nine of 14 animals dosed at 10 a.m. with Sodium Salicylate and 25 mg/kg $PGF_{2\alpha}$ died after dosing. In groups dosed with Sodium Salicylate only, the resorption rates were 9.7 or 11.8% with dosing at 10 a.m. or 2 p.m., respectively, and the respective incidences of fetuses with rib malformations were 53.6 or 37.3%. In the group dosed with Sodium Salicylate at 10 a.m. and 2.5 mg/kg $PGF_{2\alpha}$ at 12 p.m., the incidences of resorptions and fetuses with rib malformations were 4.4 and 62.8%, respectively. In the groups dosed with Sodium Salicylate at 10 a.m. and 25 mg/kg $PGF_{2\alpha}$ at 10 a.m., 12 p.m., or 2 p.m., the incidences of resorption were 74.5, 24.5, or 4.4%, respectively, and the respective incidences of fetuses with rib malformations were 100, 92.5, or 87.8%.

Groups of female Sprague-Dawley rats were fed basal diet (containing 0.15 ppm sodium selenite) or a diet containing 3.0 ppm sodium selenite for 8 wks (Bergman et al., 1990). After 8 wks, the animals were mated and groups of 16-19 gravid animals, fed either a basal or selenite-supplemented diet, were dosed i.v. using an osmotic minipump to maintain a stable Salicylic Acid blood concentration. The animals were given a daily dose on days 6-13 of gestation with 150 mg/kg Sodium Salicylate at an infusion rate of

Table 12b. Effect of Zinc on Sodium Salicylate-induced Teratogenesis in Wistar Rats (Hackman and Hurley, 1984)

Zinc (µg/g)	Salicylate (mg/kg)	# Litters	Total Viable Fetuses	Res/T (%)	Res+Mal/T (%)	Mal/Viable (%)
Zn defficient (0.4)	0	7	41	51	77	54
Zn defficient (0.4)	250	4	34	17	82	79
Zn defficient (0.4)	500	8	11	87	100	100
Zn defficient (0.4)	750	4	0	100	100	0
4.5	0	6	56	13	36	26
4.5	250	5	44	12	48	40
4.5	500	6	40	34	57	35
4.5	750	4	0	100	100	0
9	0	9	92	4	6	2
9	250	5	42	27	34	9
9	500	8	64	20	29	10
9	750	7	17	77	85	35
100	0	9	82	10	11	1
100	250	5	54	8	15	7
100	500	10	41	58	65	17
100	750	5	16	68	76	25
1000	0	10	97	10	10	0
1000	250	5	41	10	17	7
1000	500	10	58	46	50	6
1000	750	7	17	76	77	5

10 µl/h; controls were dosed i.v. with physiological saline. All animals were killed on day 19 of gestation.

Selenite did not have a reproductive or teratogenic effect on animals given physiological saline. The number of surviving fetuses (36.4% of implants and 3.6 fetuses per litter were resorbed or dead) and fetal weight (1.86 g) was decreased in animals fed the basal diet and dosed with Sodium Salicylate; malformations were observed in 5.4% of the fetuses, a total of eight malformations were observed in seven of 129 fetuses. In animals fed the selenite-supplemented diet and dosed with Sodium Salicylate, an increase in fetal survival was observed compared to the test group fed a basal diet (11.0% of implants and 1.4 fetuses per litter were resorbed or dead). The incidence of fetal malformations was decreased; 1.9% of the fetuses were malformed, and a total of six malformations were observed in three of 154 fetuses. A slight but insignificant increase in fetal weight (2.00 g) was observed in selenite supplemented animals.

Gravid Sprague-Dawley rats were used in studies examining homeostasis, teratogenic effects, and fetal histopathology (Khera, 1991). The animals were dosed s.c. with 280 mg/kg/day Sodium Salicylate, and the effects of ammonium chloride or sodium bicarbonate were determined. Dependent on the study, dosing was performed on day 8, days 8 and 9, or days 8-10 of gestation. Sodium Salicylate induced mild maternal acidosis, hypokalemia, and hypophosphatemia, with no change in pH. It also induced maternal hemorrhage in extraembryonic cavities, papillary proliferation of the visceral yolk sac endoderm, and failure to form the chorioallantoic labyrinth. Resorptions, hydrocephaly, rib defects, and fetal body weight reduction were observed. Concur-

rent treatment with ammonium chloride enhanced the teratologic and histologic effects, while concurrent treatment with sodium bicarbonate significantly reduced these effects. Neither concurrent treatment affected acid-base values.

GENOTOXICITY

IN VITRO GENOTOXICITY STUDIES

Salicylic Acid

Salicylic Acid was not mutagenic in a *Salmonella*/microsome test using *S. typhimurium* strains TA100, TA98, TA1535, and TA1537 with metabolic activation (McCann et al., 1975).

A modified Ames test was performed with 1, 10, and 100 µg/plate Salicylic Acid using *S. typhimurium* strains TA1535, TA1537, TA1538, and TA1536 (Commoner, 1976). Negative and positive controls were used. The test was performed without metabolic activation and with activation using microsome preparations from seven different tissues from Wistar rats. Salicylic Acid was not mutagenic.

Salicylic Acid was not mutagenic towards *S. typhimurium* TA100 or TA98 with or without metabolic activation (Sugimura et al., 1976; Kawachi et al., 1980a; 1980b), it was not mutagenic towards *Escherichia coli* WP-2 (Sugimura et al., 1976), and it was negative in a *Bacillus subtilis rec assay* without metabolic activation (Kawachi et al., 1980a; 1980b).

Salicylic Acid was used to determine the lethal and mutagenic effects on and the uptake by *Saccharomyces cerevisiae* strain *rad18* cells (Zetterberg, 1979). Killing and reversion frequencies were pH- and temperature-dependent. The undissociated form of Salicylic Acid was taken up more readily.

A chromosome aberration assay was performed using Chinese hamster ovary (CHO) cells with and without metabolic activation to determine the clastogenic potential of Salicylic Acid (Stich et al., 1981). A concentration of 25 mg/ml, half the level which induced mitotic inhibition, was not clastogenic with or without metabolic activation. The addition of Cu^{2+} and Mn^{2+} did not have much effect on the % metaphases with chromosome aberrations induced by 12 mg/ml Salicylic Acid; the % with Salicylic Acid only was 1.4% as compared to 1.3 and 0.0% with Cu^{2+} and Mn^{2+}, respectively.

San and Chan (1987) reported that 2.5-10.0 mg/ml Salicylic Acid was not mutagenic in an Ames assay using *S. typhimurium* strain TA98. The test was performed with and without metabolic activation. These investigators also studied the effect of 2.5-10 mg/ml Salicylic Acid on aflatoxin B_1 (AFB_1)-induced mutagenicity was determined using *S. typhimurium* strain TA98 in the presence of metabolic activation. Salicylic Acid inhibited AFB_1-induced mutagenesis when administered concurrently, but not when Salicylic Acid was added after AFB_1.

In another Ames test, 0.1 mg/disc Salicylic Acid was not mutagenic toward *S. typhimurium* TA98 with or without metabolic activation (Kuboyama and Fujii, 1992). Using strain TA100, mutagenic activity was seen with rat, but not mouse, guinea pig, or hamster, S9; no mutagenic activity was seen without metabolic activation.

A rec-assay was performed using *B. subtilis* strains H17 (Rec^+) and M45 (Rec^-) (Kuboyama and Fujii, 1992). Salicylic Acid was positive; 2 mg had a DNA-damaging tendency.

The effect of Salicylic Acid on *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-methyl-*N*-nitrosourea (MNU) mutagenicity was evaluated using *Euglena gracilis* (Foltínová and Grones, 1997). Concentrations of 50-500 µmol/l Salicylic Acid inhibited MNNG mutagenicity by 24-66.2% and of 800-1200 µmol/l inhibited MNU mutagenicity by 26-36%. A concentration of 185 µmol/l was needed to inhibit MNNG mutagenicity by 50%. Salicylic Acid, 50-1200 µmol/l, was not mutagenic to *Euglena gracilis*.

Butyloctyl Salicylate

The mutagenic potential of Butyloctyl Salicylate in DMSO was determined in a standard plate incorporation assay and a pre-incubation assay using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *E. coli* strain CM891 (WP2uvrA/pKM101) (Huntingdon Life Sciences, 1998e). Doses of ≤5000 µg/plate were tested without and with metabolic activation. Negative and positive controls gave expected results. Butyloctyl Salicylate was not mutagenic.

An *in vitro* mammalian chromosome aberration test was performed using human lymphocytes to determine the mutagenic potential of Butyloctyl Salicylate in DMSO (Huntingdon Life Sciences, 1998f). Doses of 20-500 µg/plate were tested without metabolic activation and of 500-2500 µg/plate were tested with metabolic activation. Negative and positive controls gave expected results. No reproducible increases in the frequency of metaphases with aberrant chromosomes was observed; with a 3 h treatment, 20 h sampling time, a significant increase was observed in one of two cultures treated with 2500 µg/plate with metabolic activation. It was concluded that Butyloctyl Salicylate was not clastogenic.

Ethylhexyl Salicylate

An Ames assay was performed using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 to determine the mutagenic potential of Ethylhexyl (Octyl) Salicylate (Haarmann and Reimer, 1991). Concentrations of 3000-75,000 µg/plate were tested without metabolic activation and of 100-3000 µg/plate with metabolic activation. Ethylhexyl (Octyl) Salicylate was not mutagenic.

Isodecyl Salicylate

The mutagenic potential of Isodecyl Salicylate was determined in an Ames test using *S. typhimurium* strains TA97, TA98, TA100, and TA102 (Vevy Europe, 1985). Concentrations of 312, 625, 2500, and 5000 µg/plate were tested in the presence of metabolic activation. Appropriate positive controls and a negative control were used. Isodecyl Salicylate was not mutagenic at the concentrations tested.

Methyl Salicylate

An Ames test was performed using *S. typhimurium* TA92, TA1535, TA100, TA1527, TA94, and TA98 with metabolic activation (Ishidate et al., 1984). Methyl Salicylate, ≤10 mg/plate, was not mutagenic.

The mutagenic potential of 1.0-333.3 µg/plate Methyl Salicylate was determined in a *Salmonella*/mammalian microsome assay using strains TA1535, TA1537, TA98, and TA100 with and without metabolic activation (Mortelmans et al., 1986). Positive and negative controls were used. Methyl Salicylate was not mutagenic.

Methyl Salicylate, 0.1 mg/disc, was not mutagenic in an Ames test using *S. typhimurium* TA98 and TA100 without metabolic activation, but it was mutagenic towards TA98 and TA100 in the presence of hamster, but not rat, mouse, or guinea pig, S9 (Kuboyama and Fujii, 1992). Five mg/disc was negative for DNA damage in a rec assay.

Sodium Salicylate

The mutagenic potential of 1-3% Sodium Salicylate was determined using *E. coli* (Demerec et al., 1951). Sodium Salicylate was not mutagenic.

Sodium Salicylate was negative in a DNA-cell-binding assay using Ehrlich ascites cells (Kubinski et al., 1981).

Sodium Salicylate, 0.1 mg/disc, was not mutagenic in an Ames test using *S. typhimurium* TA98 and TA100 with or without metabolic activation, and 5 mg/disc was negative for DNA damage in a rec assay (Kuboyama and Fujii, 1992).

The effect of Sodium Salicylate on MNNG and MNU mutagenicity was evaluated using *Euglena gracilis* (Foltínová and Grones, 1997). Concentrations of 50-500 µmol/l Sodium Salicylate inhibited MNNG mutagenicity by 38-74% and of 800-1200 µmol/l inhibited MNU mutagenicity by 34-42%. Concentrations of 85 and 1150 µmol/l were needed to inhibit MNNG and MNU mutagenicity, respectively, by 50%. Sodium Salicylate, 50-1200 µmol/l, was not mutagenic to *Euglena gracilis*.

Tridecyl Salicylate

The mutagenic potential of Tridecyl Salicylate was determined in a *S. typhimurium* reverse mutation assay using *S. typhimurium* strains TA1535, TA1537, TA1538, TA97, and TA98 (Biolab, 1997a). Concentrations of 10-10,000 µg/plate in DMSO were tested in the presence and absence of metabolic activation. Appropriate positive controls and a negative control were used. Tridecyl Salicylate was not mutagenic at the concentrations tested.

IN VIVO GENOTOXICITY STUDIES

Salicylic Acid

Three of four male mice were dosed orally with 100 mg/kg Salicylic Acid; the effects on incorporation of tritiated thymidine into testicular DNA was investigated (Seiler, 1977). Salicylic Acid significantly decreased thymidine incorporation compared to controls.

A sister chromatid exchange (SCE) study was performed using groups of five male Swiss albino mice to determine the clastogenic potential of Salicylic Acid (Giri et al., 1996). The animals were injected i.p. with 25, 50, or 100 mg/kg Salicylic Acid in DMSO 1 h after s.c. implantation of a 5-bromodeoxyuridine (BrdU) tablet or dosed orally with 350 mg/kg Salicylic Acid in 2% gum acacia in distilled water 0.5 h after tablet implantation. Negative controls were dosed with 75 µl DMSO (i.p.) or 0.3 ml gum acacia (orally) and positive controls were dosed with 1.5 mg/kg mitomycin C. Colchicine was injected i.p. 22 h after BrdU-tablet implantation, and bone marrow was removed 2 h later. Salicylic Acid did not induce SCEs.

Giri et al. (1996) also performed a chromosome aberration study using male Swiss albino mice. Groups of four animals were dosed i.p. with 50, 100, or 200 mg/kg Salicylic Acid in DMSO and five animals were dosed orally with 350 mg/kg Salicylic Acid in 2% gum acacia in distilled water. Groups of four and five negative control animals were dosed i.p. with 75 µl DMSO or orally with 0.3 ml 2% gum acacia in distilled water, respectively; five positive control animals were dosed with 25 mg/kg cyclophosphamide. The animals were injected with 2 mg/kg colchicine 22 h after dosing, and killed 2 h later. In both the i.p. and oral studies, no significant increase in chromosomal aberrations was seen with any dose of Salicylic Acid. A significant increase in mitotic index was observed with the 50 mg/kg i.p. dose and the single oral dose.

Ethylhexyl Salicylate

The mutagenic potential of Ethylhexyl (Octyl) Salicylate was determined in a micronucleus test performed according to OECD Test Guideline No. 474 (Haarmann and Reimer, 1991). Five male and five female NMRI mice were dosed orally with 2 g/kg Ethylhexyl (Octyl) Salicylate. No increase in micronucleated polychromatic erythrocytes was observed 24, 48,or 72 h after dosing.

Sodium Salicylate

A SCE assay was performed using male Swiss albino mice following the procedure described previously (Giri et al., 1996). Sodium Salicylate was given i.p. at doses of 25, 50, or 100 mg/kg and orally as a single 350 mg/kg dose. Sodium Salicylate did not induce SCEs.

A chromosomal aberration study was also performed using male Swiss albino mice following the procedure described previously (Giri et al., 1996). Sodium Salicylate was given i.p. at doses of 50, 100, or 200 mg/kg and orally as a single 350 mg/kg dose. A significant increase in chromosomal aberrations was seen with the 200 mg/kg i.p. dose and the 350 mg/kg oral dose.

CARCINOGENICITY

Salicylic Acid

Salicylic Acid was reported by Sugimura et al. (1976) and Kawachi et al. (1980) not to be a carcinogen, although details were not provided.

The effect of Salicylic Acid on mouse epidermal JB6 cells, a culture model used to study tumor and anti-tumor promotion, was examined (Dong et al., 1997). Salicylic Acid inhibited tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced transformation in a concentration-dependent manner. No significant effect was observed on ^{3}H-TdR incorporation into DNA. Salicylic Acid inhibited TPA-induced tissue inhibitor of metalloproteinase (TIMP-1) mRNA expression, and it inhibited in a dose-dependent manner the anchorage-independent growth of H-*ras*^{12} and c-*jun*-transformed JB6 cells. Salicylic Acid did not affect the protein concentrations of mitogen-activated protein kinase Erk1 or Erk2, even with 24 h pretreatment. Salicylic Acid decreased intracellular pH. The researchers stated that the results "suggest that inhibition of tumor promoter induced-neoplastic transformation in JB6 cells may be through inhibition of AP-1 [activator protein-1] transactivation."

Methyl Salicylate

A skin painting study was performed in which Methyl Salicylate was applied to the back of 39 mice at biweekly intervals for 400 days (Burdette and Strong, 1941). No neoplasms were induced.

Groups of 15 male and 15 female A/He mice were dosed i.p. with 100 or 500 mg/kg Methyl Salicylate in tricaprylin three times per wk for 8 wks for a total of 24 doses (Stoner et al., 1973). Two negative control groups, one untreated and one dosed with vehicle, and two positive control groups, given 5 or 20 mg/animal urethan, were used. The animals were killed 24 wks after the initiation of dosing. Two out of 13 males and 1/14 females of the low dose group that survived until study termination had lung tumors. One out of 12 males and 5/13 females of the high dose group that survived until study termination had pulmonary tumors. These compare to 10/46 males and 8/48 females and 8/30 males and 10/28 females with tumors in the untreated and vehicle control groups, respectively.

Sodium Salicylate

Elder et al. (1996) reported that Sodium Salicylate had dose-dependent inhibitory effects on adenoma, *in vitro* transformants of adenoma, and carcinoma cell lines, with IC_{50} values (not defined) of 1.65-7.28 mM. The carcinoma and *in vitro*-transformed adenoma cell lines were more sensitive than the adenoma cell lines.

CLINICAL ASSESSMENT OF SAFETY

IRRITATION STUDIES ON NORMAL SKIN

Salicylic Acid

The irritation potential of a gel containing 2% Salicylic Acid was determined in a cumulative irritation study completed by 27 subjects, 15 males and 12 females (Harrison Research Laboratories, Inc. [HRL], 1993a). An occlusive patch containing 0.2 g of the test material was applied to the back of each subject for 48 (Monday and Wednesday) or 72 h (Friday) three times per wk for 2 wks for a total of six applications. Upon patch removal, the test sites were scored (on a scale of 0-4) and the new patches were applied.

The six daily scores were summed to yield an aggregate 14-day score, and the 14-day scores for all subjects were summed to yield a grand total score. The grand total score for the gel containing 2% Salicylic Acid was 14.5, and the gel produced "minimal cumulative irritation".

The irritation potential of a facial cosmetic cream containing 1.5% Salicylic Acid (pH 2.75; Procter and Gamble Company, 1999b) was determined in a 21-day cumulative irritation patch test (TKL Research, Inc., 1998a). Twenty-seven subjects completed the study. Distilled water and 0.2% (w/v) SLS served as negative and positive controls, respectively. Occlusive patches containing 0.2 g of the test material were applied to the infrascapular area of the back of each subject for 24 (Monday-Thursday) or 72 h (Friday); the test sites were scored upon patch removal and new patches were applied to the same site. This procedure was repeated for 21 days.

A total score was calculated by summing each individual's scores on each of the 21 days. Normalized scores were calculated by summing the scores of all subjects, dividing by the total number of readings for all subjects, and multiplying by 21 (the number of readings) and by 10 (to normalize to 10 subjects). A facial cosmetic cream containing 1.5% Salicylic Acid, with a total score of 415.0 and a normalized score of 147.5, was classified (using the normalized score) as slightly irritating.

A 21-day cumulative irritation patch test was performed following the same procedure described above for a facial skin conditioner cream containing 1.5% Salicylic Acid (pH 2.78; Procter and Gamble Company, 1999b) and a facial skin conditioner lotion containing 0.02% Salicylic Acid (pH 3.5; Procter and Gamble Company, 1999b), with the exception that the cream was applied under occlusive and semi-occlusive patches and the lotion was applied under a semi-occlusive patch (TKL Research, Inc., 1998b). Twenty-seven subjects completed the study.

Under occlusive patches, the cream containing 1.5% Salicylic Acid had total and normalized irritation scores of 125.0 and 45.7, respectively. Using semi-occlusive patches, the cream containing 1.5% Salicylic Acid had total and normalized scores of 45.0 and 16.5, respectively. Under both test conditions, the cream was classified using the normalized scores as producing no significant irritation. The lotion containing 0.02% Salicylic Acid had total and normalized scores of 50.0 and 18.3, respectively, and it also was classified as producing no significant irritation.

A third 21-day cumulative irritation patch test was performed using the same procedure (TKL Research, Inc., 1998c). Twenty-eight subjects completed the study. A facial skin conditioner cream containing 1.5% Salicylic Acid (pH 2.78; Procter and Gamble Company, 1999) was tested using occlusive and semi-occlusive patches. Using occlusive patches, the cream had total and normalized scores of 381.0 and 132.0, respectively, and was slightly irritating (classified using the normalized scores). Using semi-occlusive patches, it had total and normalized scores of 69.0 and 23.9, respectively, and was classified as producing no significant irritation.

Ethylhexyl Salicylate

A 48-h occlusive patch test was performed using 4% Ethylhexyl (Octyl) Salicylate in petrolatum (Anonymous, 1976). Ethylhexyl (Octyl) Salicylate was not irritating.

Methyl Salicylate

In a 48 h closed-patch test, 8% Methyl Salicylate in petrolatum did not produce irritation (Opdyke, 1978).

In a dermal absorption study described earlier in which five subjects applied products containing 12-50% Methyl Salicylate (Roberts et al., 1982), each subject reported pain and erythema at the application site of each product.

Erythema determinations were made on four subjects using thermography in a dermal penetration study (Collins et al., 1984). A product containing 1% w/w Methyl Salicylate was applied as a metered aerosol. A visible erythematous reaction developed within approximately 10 min of application.

In another dermal absorption study described earlier (Morra et al., 1996) in which six male and six female subjects applied an ointment containing 12.5% Methyl Salicylate twice daily for four days, all subjects reported burning, stinging, and erythema at the site of application. All but one subject reported pruritus and prolonged erythema for up to 7 days after the termination of dosing.

Methyl Salicylate was a primary contact irritant when tested in an unspecified protocol (Wilmer et al., 1994).

TEA-Salicylate

One subject included in a dermal absorption study (described previously) reported prolonged pruritus and erythema (Morra et al., 1996). In the study, 12 subjects, six males and six females, applied two doses of a cream containing 10% TEA-Salicylate with a 12 h interval.

Tridecyl Salicylate

The dermal irritation potential of Tridecyl Salicylate was determined using 30 male and female subjects (number per sex not stated) in an occlusive patch test performed according to the methods of Draize (Biolab, 1997b). The patch was applied to the volar forearm of each subject for 48 h, and the test sites were scored 15 min and 24 h after patch removal. No erythema or edema was observed, and the total irritation and mean irritation indices were 0 at both evaluations. Tridecyl Salicylate was a non-irritant.

IRRITATION STUDIES ON DISEASED SKIN

Methyl Salicylate

Occlusive patch tests were performed on five herbal topical medicines using 20 subjects with endogenous eczema or contact dermatitis (Lee and Lam,, 1990). The oils or ointments contained 3.75-67% Methyl Salicylate. One oil containing 67% Methyl Salicylate caused irritation in eight of the subjects and an oil containing 40% Methyl Salicylate caused irritation in two of the subjects. The remaining oils and ointment, containing 15, 38, and 3.75% Methyl Salicylate, respectively, did not produce any irritant responses.

EFFECT ON IMMEDIATE CONTACT REACTIONS TO OTHER AGENTS

Salicylic Acid

The effect of a 5% Salicylic Acid gel on non-immunologic immediate contact reactions (NIICRs) to 500 mM benzoic acid, 500 mM cinnamic aldehyde, 50 mM methyl nicotinate, and 14.1 M (100%) DMSO was examined using 16 subjects, eight males and eight females, five of which were atopic (Johansson and Lahti, 1988). On day 1, open applications of 10 µl of the irritants were applied to 1 x 1 cm areas on the

back of each subject. A 0.5 ml dose of 5% Salicylic Acid was applied to a 10 x 15 cm area at 0, 8, and 24 h. One h after the last application, the NIICR test was done on the gel area and the reference area. The test was repeated the next day (day 3) on the same areas but not on the previous test sites. The test sites were wiped 20 min and observed 40 min after application. Reactions were assessed visually and with a laser-Doppler flowmetry (LDF) device. Erythema due to benzoic acid and methyl nicotinate was significantly reduced with Salicylic Acid on days 2 and 3 when assessed using LDF. Upon visual observation, reactivity to cinnamic aldehyde was reduced on day 3; Salicylic Acid did not affect edema.

SENSITIZATION

Fisher (1986) reported that a subject can have an allergic contact dermatitis reaction to a product, but not react to any of the individual ingredients. This can be due to a "physical synergism", in which one ingredient can act as a "penetrating agent", or a "chemical synergism", in which individual nonsensitizing ingredients combine to form a contact allergen. Salicylic Acid was used as an example of an ingredient that can promote skin penetration and be involved in physical synergism. However, an ingredient can also "quench" the allergenic capacity of a product.

Studies of sensitization reactions in study subjects with normal skin (predictive studies) and with diseased skin (provocative studies) of the salicylates are presented below.

Predictive Studies

Salicylic Acid

A maximization study was performed using 25 subjects; induction and challenge concentrations of Salicylic Acid were 20 and 10%, respectively (Kligman, 1966). None of the subjects were sensitized.

Two repeated insult patch tests (RIPTs) were performed to evaluate the sensitization potential of moisturizer cream or lotion containing 2% Salicylic Acid. In the first study evaluating the sensitization potential of a cream, 114 subjects, 20 males and 94 females, enrolled in and 99 subjects, 16 males and 83 females, completed the study (TKL Research, Inc., 1993a). None of the subjects discontinued for test article-related reasons. Two-tenths of a gram of the test material was applied to occlusive patches, and the patches, which were air-dried for 15-30 min, were applied to the infrascapular region of the back for 24 h. This procedure was repeated every 48-72 h after patch application for a total of nine applications. After a 2-wk non-treatment period, a challenge patch was applied to a previously untreated site on each subject. The patches were removed at 24 h and the sites evaluated 48 and 72 h after application. The only responses seen, i.e., "?" - doubtful response, barely perceptible erythema, only slightly different from surrounding skin and "+" - definite erythema without edema, were observed during induction. A moisturizer cream containing 2% Salicylic Acid was not a sensitizer.

In the second RIPT, the sensitization potential of both a moisturizing cream and a moisturizing lotion containing 2% Salicylic Acid was determined (TKL Research Inc., 1993b; 1993c). Of the 119 subjects, 14 males and 105 females, enrolled in the study, 101 subjects, 12 males and 89 females, completed the study; half of the subjects had "self-professed sensitive skin". None of the subjects discontinued for test article-related reasons. The procedure was the same as described previously. With both products, "?" and "+" were the only reactions observed during induction. Neither the cream nor the lotion was a sensitizer.

A RIPT was performed to determine the sensitization potential of a gel containing 2% Salicylic Acid (HRL, 1993b). The test was completed by 193 subjects, 52 males and 141 females. Occlusive patches containing 0.2 g of the test material were applied for 24 h to the left upper back of each subject three days per wk for 3 wks for a total of nine induction patches. The test sites were scored on a scale of 0-4 at 24 (Monday and Wednesday patches) or 48 h (Friday patches) after patch removal. Following a 2-wk non-treatment period, the challenge was performed by applying a 24 h occlusive patch to a previously untreated site on the right upper back of each subject. The induction and challenge sites were scored upon removal of the patch, and a patch was again applied to the challenge site. The sites were scored 48, 72, and 96 h after application of the initial challenge patch. During induction, five subjects had scores of ± (faint, minimal reaction) or 1 (erythema), and during challenge, seven subjects had scores of ± or 1. A

gel containing 2% Salicylic Acid was not a sensitizer.

A second RIPT of a gel containing 2% Salicylic Acid was completed with 198 subjects, 59 males and 139 females, following the same procedure with the exception that only one challenge patch was applied (HRL, 1997a). During induction, two subjects had ± reactions, and during challenge, five subjects had reactions of ± or 1. A gel containing 2% Salicylic Acid was not a sensitizer.

Ethylhexyl Salicylate

A maximization test was performed using 23 subjects to determine the sensitization potential of 4% Ethylhexyl (Octyl) Salicylate in petrolatum (Anonymous, 1976). No sensitization reactions were observed.

Methyl Salicylate

In a maximization test using 27 subjects, 8% Methyl Salicylate in petrolatum produced no sensitization reactions (Opdyke, 1978).

Provocative Studies

Salicylic Acid

A group of 230 patients, 72 males and 158 females, with venous leg eczema were patch tested with 5% Salicylic Acid in vaseline (Thune, 1969). The patches were applied to the back or anterior aspect of the thigh for 24 h and read daily for 4 days. Three patients had positive reactions (defined as erythema and infiltration for >24 h after patch removal).

Wojnar et al. (1980) examined the augmentation of allergic histamine release from human leukocytes by several anti-inflammatory/analgesic agents, including Sodium Salicylate. Leucocyte donors (9 women and 7 men) were selected on the basis of release of histamine from their leukocytes with ragweed or housedust extracts. A 25% augmentation of ragweed-induced histamine release was considered significant and was used as a common basis for comparison. The authors report that a concentration of 120 ± 29 µM Sodium Salicylate is needed to produce a 25% augmentation of ragweed-induced histamine release (as compared to 917 ± 104 µM aspirin, for example).

Salicylic Acid, 5% in petrolatum, was part of a standard patch test battery from 1979 to 1983 (Goh and Ng, 1986). Of 9701 patients patch-tested, 11 (doubtful) positives were observed. Repeat patch tests were performed with eight of these 11 patients using 0.5, 1, 2, and 5% Salicylic Acid. One patient, who had a history of immediate type hypersensitivity to oral salicylates, had a positive reaction to 1, 2, and 5% Salicylic Acid.

Twenty-seven patients, 13 males and 14 females, with a sensitivity to aspirin were challenged orally with Salicylic Acid (Zhu et al., 1997). The challenge was performed with 25-400 mg Salicylic Acid. The challenge was negative for all patients.

Sodium Salicylate

The allergenic potential of Sodium Salicylate was determined in a number of studies using up to 31 patients, 19 males and 12 females, with a history of aspirin intolerance (Patriarca et al., 1976). In a skin test, 31 patients were given an intradermal injection of 0.02 ml of 0.1% Sodium Salicylate; the results were scored 20 min after dosing. In a Prauxnitz and Küstner passive transfer test (PK test), 23 patients were used and 0.1% Sodium Salicylate was the challenge concentration for passively sensitized sites (0.1 ml serum). A passive cutaneous anaphylaxis (PCA) test with 0.05 g Sodium Salicylate was used to determined $IgG_{1,3,4}$ antibodies in all 31 patients; three guinea pigs were used in each case to confirm the reaction. A lymphocyte transformation test (LTT) was performed *in vitro* using 26 patients, and 2-^{14}C-thymidine was employed. There was one positive reaction to Sodium Salicylate in the skin test, none in the PK test, two in the PCA test (scores not defined), and two in the LTT test.

PHOTOTOXICITY/ PHOTOSENSITIZATION

Salicylic Acid

The phototoxic potential of a cream containing 2% Salicylic Acid was determined using five male and five female subjects with type I-III skin (Ivy Laboratories, 1993a). Duplicate 2 cm x 2 cm occlusive patches containing 0.2 g of the cream, which were allowed to air dry for 15-30 min, were applied to the lower back of each subject. A third site which was treated in a similar manner with hydrophilic ointment served as a control. Twenty-four h after application, one of the test patches

and the control patch were removed, and the sites were exposed to 20 J/cm^2 of UVA (320-400 nm, peak at 350 nm). A 150 W compact xenon arc source with a UV-reflecting dichroic mirror, a 1 mm thick Schott WG-345 filter, and a 1 mm thick UG11 filter served as the light source. UV irradiance was measured at the skin. The second test patch was then uncovered and served as an unirradiated treated control.

The sites were graded at the end of each exposure and 24 and 48 h after irradiation. The authors reported that no phototoxicity was observed, and the concluded that the cream containing 2% Salicylic Acid did "not possess a detectable phototoxicity potential in humans."

The phototoxic potential of a gel containing 2% Salicylic Acid was determined in a test completed by 10 subjects, one male and nine females, with type I, II, or III skin (HRL, 1993c). Duplicate occlusive patches containing 0.2 g of the test material were applied to the volar forearms of each subject. The patches were removed 24 h after application and the sites were scored on a scale of 0-4. One forearm was then irradiated with UVA light for 15 min. The light source consisted of a set of four F40BL fluorescent tubes with a wavelength range of 320-400 nm, with >95% of the relative energy at 360 nm; the dose was measured as 0.22 J/cm^2/min (total dose of 3.3 J) at a distance of 15 cm. Immediately, 24 h, and 48 h after irradiation, the test sites on each forearm were scored. No reactions were observed at the irradiated nor non-irradiated sites, and a gel containing 2% Salicylic Acid was not phototoxic.

Another phototoxicity test was performed on a gel containing 2% Salicylic Acid following the same procedure, with the exception that the sites were irradiated for 17 min and were scored immediately and 24, 48, and 72 h after irradiation (HRL, 1997b). Ten subjects, two males and eight females, completed the test. The UVA light source consisted of four F40BL fluorescent tubes with approximately 95% of the output in a range of 320-400 nm; the dose was measured as approximately 3.1±0.3 mW/cm^2 (total dose of 3.2±0.3 J) at a distance of 15 cm. One subject had a ± (faint, minimal erythema) reaction at both the irradiated and non-irradiated test sites and one had a ± reaction at the non-irradiated site. A gel containing 2% Salicylic Acid was not phototoxic.

A photocontact allergenicity test was performed using 25 subjects, eight males and 17 females, to determine the photosensitization potential of a cream containing 2% Salicylic Acid (Ivy Laboratories, 1993b). Each subject's minimal erythema dose (MED) was determined. Occlusive 2 cm x 2 cm occlusive patches containing 100 mg of the test material (25 mg/cm^2), which was allowed to air dry for 15-20 min, were applied to the lower back of each subject for 24 h. The patches were removed, and the sites were exposed to 3 MEDs from a 150 W compact solar arc simulator equipped with a UV-reflecting dichroic mirror, a 1 mm thick Schott WG-320 filter (290-400 nm), and a 1 mm thick UG11 filter. Total irradiance at the skin was measured.

Forty-eight h after irradiation, patches were reapplied to the same sites and the procedure was repeated. Induction consisted of twice weekly exposures for 3 wks. A challenge was performed 10 days after the last induction exposure by applying for 24 h duplicate occlusive patches containing 25 mg/cm^2 of the test material to previously untested sites on the back. One patch was removed, and the site was irradiated with 4 J/cm^2 UVA. The second site served as a treated unirradiated control. The test sites were examined 48 and 72 h following UVA exposure. No abnormal responses were observed, and the researchers concluded that the cream containing 2% Salicylic Acid did "not possess a detectable photocontact-sensitizing potential in human skin."

A second photocontact allergenicity test was performed using 25 subjects, one male and 24 females, to again evaluate the photosensitization potential of a cream containing 2% Salicylic Acid (Ivy Laboratories, 1993c). The procedure described above was generally followed. However, in this test, 0.2 mg of the test material was applied to the patch, and the patch was allowed to air dry for 15-30 min prior to application. No unexpected responses were observed; mild to moderate erythema, scaling, and tanning, which can be expected following repeated UV exposure, were observed. The researchers concluded that a cream containing 2% Salicyiic Acid did "not possess a detectable photocontact-sensitizing potential in human skin."

The photoallergic potential of a gel containing 2% Salicylic Acid was determined in a test completed by 28 subjects, four males and 24 females, with type I, II, or III skin (HRL, 1993d). During induction, an occlusive patch containing 0.2 g of the

test material was applied for 24 h to the radial aspect of the volar forearm (that was to be irradiated) twice per wk for three wks for a total of six applications. A second patch was applied either to the opposite forearm or the left scapular area of the back, as determined by the subject, and this site was not irradiated. Upon patch removal, the test sites were scored on a scale of 0-4, and the appropriate sites were irradiated with UVA and UVB. UVA irradiation was for 15 min. UVB irradiation was based on skin type and MED and was either two MEDs or a maximum of 135 sec. The test sites were scored immediately after irradiation. Following a 14-day non-treatment period, the ulnar aspect of the irradiated forearm served as the challenge site and a patch was applied for 24 h to a previously untreated site. For challenge of the non-irradiated site, the patches were applied for 24 h as appropriate to either the ulnar aspect of the forearm or the right scapular area of the back. Following patch removal, the sites were scored and the appropriate forearm was subjected to UVA irradiation only. The test sites were scored immediately, 24 h, and 48 h after irradiation.

The UVA light source consisted of a set of four F40BL fluorescent tubes with a wavelength range of 320-400 nm and >95% of the relative energy at 360 nm; the dose was measured as approximately 0.22 J/cm^2/min (for a total dose of 3.3 J) at a distance of 15 ± 2 cm. UVB was from the "Solarium 300", with a wavelength range of 260-320 nm and >95% of the relative energy at 300 nm; the dose was measured at approximately 1.2 mJ/cm^2/sec (skin type I: 105 sec = 126mJ; skin type II: 120 sec = 144 mJ; skin type III: 135 sec = 162 mJ) at a distance of 22 ± 2 cm.

During induction, 14 subjects had reactions of ± (minimal erythema) or 1 (erythema and/or slight edema within patch margins) at the irradiated test site and one subject had a ± reaction at the non-irradiated test site. Twelve subjects had reactions of ± or 1 at the irradiated control site. At challenge, one subject had a reaction of 1 at the irradiated and non-irradiated test sites. A gel containing 2% Salicylic Acid "did not induce contact dermal photoallergy nor contact dermal sensitization in human subjects" (HRL, 1993d).

The photoallergic potential of a gel containing 2% Salicylic Acid was determined in a second study completed by 28 subjects, five males and 23 females, that generally followed the same procedure (HRL, 1997c). UVA irradiation was 17 min and UVB irradiation was either 2 MED or a maximum of 120 sec. The UVA light source consisted of a set of four F40BL fluorescent tubes with approximately 95% of the output in the wavelength range 320-400 nm; the dose was measured as approximately 3.1±0.3 mW/cm^2 (for a total dose of 3.2 ± 0.3 J) at a distance of 15 ± 2 cm. UVB was from the "Solarium 300", with a wavelength range of 260-320 nm and >95% of the relative energy at 300 nm; the dose was measured at approximately 1.2 ± 0.1 mW/cm^2 (skin type I: 90 sec = 108 mJ; skin type II: 105 sec = 126 mJ; skin type III: 120 sec = 144 mJ) at a distance of 22 ± 2 cm. The opposite volar forearm only served as the non-irradiated site. During induction, 21 subjects had reactions of ± (minimal erythema) or 1 (erythema within patch margins) at the irradiated test site and two subjects had ± reactions at the non-irradiated test site. Also during induction, seven subjects had reactions of ± or 1 at the irradiated control site. During challenge, two subjects had reactions of ± at the irradiated test site. The authors stated that the test material (containing 2% Salicylic Acid) "did not induce contact dermal photoallergy nor contact dermal sensitization in human subjects."

PHOTOPROTECTIVE EFFECTS

Salicylic Acid

The photoprotective effect of Salicylic Acid was evaluated (Kristensen and Kristensen, 1991). *In vitro*, a cream containing 2% Salicylic Acid absorbed in the 295-323 nm range, with a peak around 303 nm. *In vivo*, a test was performed using five subjects. Each subject's MED was determined following irradiation with two Philips TL 40 W/12 (UVB) lamps. Application of 0.5-10% Salicylic Acid prior to UV exposure dose-dependently inhibited UV-induced erythema. Application after UV-exposure had no effect.

Ethylhexyl Salicylate

In a study to evaluate the photoprotection ability of a formulation containing Ethylhexyl (Octyl) Salicylate, subjects were first photosensitized to UVA irradiation by ingestion of 0.6 mg/kg 8-MOP (Gange et al., 1986). After 1.5 h, 2 µl/cm^2 of a formulation containing 5% Ethylhexyl (Octyl) Salicylate, 7% padimate O, and 3% oxybenzone or the vehicle only was applied to a 2 x 10 cm area of the lower part of the back, and an untreated area served as an unprotected control.

The test areas were covered with foil, and 2 h after 8-MOP ingestion, the sites were exposed to a series of nine or 10 increasing doses of 1.0-21 J/cm^2 UVA. The light source was a bank of twelve 36" UVA tubes with peak emission at 366 nm and 98% of the UV in the range of 320-400 nm; irradiance at the skin was 4.9-5.1 mW/cm^2. The erythemal response at each site was evaluated 48 and 72 h after UV exposure, and the amount of pigmentation at each site was determined 2 wks after exposure. No erythema was seen in the unprotected controls exposed to 21 J/cm^2 UVA. The mean phototoxic protection factor (PPF) for the Ethylhexyl (Octyl) Salicylate formulation, calculated as the minimal phototoxic dose (MPD) of protected skin/MPD of unprotected skin, was 2.9 at 48 h (28 subjects) and 2.9 at 72 h (34 subjects). The PPF ranged from 1.4-7.5 at 48 h and from 0.7-7.5 at 72 h. For the vehicle controls, the mean PPF was 1.1 at 48 h (37 subjects), with a range of 0.5-2.0, and 1.1 at 72 h (38 subjects), with a range of 0.7-2.0. After 12-18 days, the melanogenic protection factor (MPF) for the Ethylhexyl (Octyl) Salicylate formulation, calculated as the minimal melanogenic dose (MMD) of protected skin/MMD of unprotected skin, was 2.7 (28 subjects), with a range of 0.7-5.4. For the vehicle controls, the mean MPF was 1.0 (36 subjects), with a range of 0.5-2.0.

URTICARIAL REACTIONS

Salicylic Acid

Eighteen of 21 subjects that had urticarial reactions to ingested aspirin were given Sodium Salicylate (Moore-Robinson and Warin, 1967). Urticaria was exacerbated in 13 of the 18 subjects.

Doeglas (1975) performed a provocative test in 20 aspirin-sensitive patients with chronic urticaria. Six of the 20 patients had positive reactions to Sodium Salicylate.

The ability of 5% Salicylic Acid in petrolatum to induce non-immunological contact urticaria was examined using 110 patients, 67 males and 43 females; 36, 23, 26, and 25 of the patients were atopic, urticarial, non-atopic, and non-allergic, respectively (Lahti, 1980). The potential of 5% Salicylic Acid in petrolatum to induce urticaria was also determined using the chamber method with 138 dermatological patients, 63 males and 75 females; 84 of the patients were atopic and 54 were non-atopic (Lahti, 1980). With this method, Salicylic Acid was applied to the backs of the patients for 20 min, and the reactions were scored 10 min after removal. No immediate reactions were seen.

OTHER SKIN EFFECTS

Salicylic Acid

The effect of vehicle on the time required for Salicylic Acid to have keratolytic action on normal human skin was investigated (Strakosch, 1943). Ointments containing 1-15% Salicylic Acid were prepared using the following six vehicles: petrolatum; petrolatum and hydrous wool fat; a base consisting of 6% of a group of esters of cholesterol (primarily oxycholesterol) in a petrolatum base; a base of fatty acid esters of diethanolamine (DEA) with petrolatum; a stearyl alcohol, liquid petrolatum, water, light petrolatum base; and a zinc oxide, talc, petrolatum base. Using groups of four subjects, open applications of the test materials were made to a 5 cm x 5 cm site on the anterior aspect of the upper thigh or on the abdomen daily three times per day for 24, 48, or 72 h or 7, 10, or 14 days. Keratolytic changes were first seen with the oxycholesterol-petrolatum base, the fatty acid esters of DEA base, and the stearyl alcohol-containing base, next with the petrolatum and hydrous wool fat base, next with the petrolatum base, and then with the zinc oxide base. The changes generally occurred more quickly with greater concentrations of Salicylic Acid.

Creams and ointments containing 2, 4, 6, or 12% Salicylic Acid were applied to the skin of the upper limbs of four subjects per group for 1 wk (Marks et al., 1975). A control group was treated with vehicle only. Skin biopsies were taken. None of the creams caused an increase in mean labeling index or mean epidermal thickness compared to controls, but a progressive increase was seen with the ointments. However, marked changes in the stratum corneum were seen with the creams; in scanning electron micrographs, wide intercellular gaps were found and surfometric analysis was indicative of an irregular surface contour.

Twenty-three subjects were used to determine the effect of 2, 4, 6, 8, 10, or 12% Salicylic Acid in aq. cream or 2, 6, or 10% Salicylic Acid in white soft paraffin on the skin (Davies and Marks, 1976).

The test materials were applied to either the inner aspect of one arm or the lateral aspect of one thigh. The appropriate vehicle was applied to a contralateral site as a control. The materials were applied twice daily and rubbed into the skin for 1 min; the sites were not occluded.

After 1 wk, the test areas were biopsied. No differences in the samples were seen upon microscopic examination. In treated cryostat sections, differences were found between the treated and control sites; the treated sites had an irregular and much thinner stratum corneum. The mean epidermal thickness was similar for test and control sites. No differences in labeling indices from tissue incubated with tritiated thymidine were seen between the treated and respective control groups. However, a significant difference was found in the labeling index of the cream and paraffin controls; the values were 7.6 and 5.7, respectively. No differences in labeling were seen between test and control specimens of the 2% Salicylic Acid in cream or 10% Salicylic Acid in paraffin groups incubated with tritiated histidine or cytidine.

In scanning electron micrographs of skin surface biopsies, differences were found between treated and control sites, especially at the greater concentrations of Salicylic Acid. The test samples had marked irregularity in the overall arrangement of the horny layer, with many irregular and loose lamellae composed of several squames, and irregularity occurred in scale apposition with large gaps (3-10 μm) between individual squames. The researchers postulated that "salicylic acid preparations enhance desquamation by encouraging squame separation by causing the dissolution of intercellular cement material."

The effect of Salicylic Acid on the stratum corneum was determined by measuring desquamation, thickness, and mitotic activity (Roberts et al., 1980). First, 6% Salicylic Acid in 70% alcohol was applied to the forearm of five subjects two males and three females, that were without generalized skin disorders or systemic disease. 70% alcohol was applied to the other arm as a control. 'Forced' desquamation corneocyte counts using a hand-held scrub apparatus were taken from different sites 1, 2, 3, 4, 6, and 8 h after application.

In a second study, the 6% Salicylic Acid in acid was applied twice daily to the forearms of the five aspect of the forearms of six subjects, one male and five females, that were without skin disorders or systemic disease; again, 70% alcohol was applied to the opposite arm as a control. Prior to the initial application, a 1 cm^2 portion of the test area was stained with a 1% aq. silver nitrate solution reduced with a photographic developer, and 24 h prior to the initial application, 5% dansyl chloride was applied to both forearms under an occlusive patch. 'Forced' desquamation was performed on days 2, 4, 6, 8, and 10. The gray-black area that resulted from the application of silver nitrate was photographed every 2 h daily until the "abnormal" color faded. The density of the stain on the photographic negative was measured. To determine the turnover time, the areas treated with dansyl chloride were examined daily with a UV lamp that emitted primarily in the UVA region until fluorescence disappeared. A 4 mm punch biopsy was taken from the treated and control site.

In the first study, the 'forced' desquamation cell count increased on the test arm until the 3 h reading (from 96.8 to 140.2 cells/cm^2/10 sec x 10^3), then it decreased, while on the control arm the cell count decreased slightly (from 100.6 to 99.4 cells/cm^2/10 sec x 10^3) until the 2 h reading, then it increased slightly. In the second study, there was a marked persistent decrease in desquamation at the test site, while on the control arm, the corneocyte count initially decreased but reached normal values after 4 days. The difference in corneocyte count between the test and control arms was significant on days 6, 8, and 10.

The results of the silver nitrate densitometry technique indicated that the stain was released more rapidly from the treated site than the control site, but the difference was not significant. No significant difference in the loss of fluorescence due to dansyl chloride was observed between the test and control sites (16 vs. 15.2 days, respectively). The biopsies indicated that the Salicylic Acid treated sites had a much thinner stratum corneum (mean 16.1, units not stated; the mean prior to treatment was 23.3) than the control sites (mean 22). No significant difference in the labeling indices of autoradiographs derived from tissues incubated with tritiated thymidine was seen.

The effect of Salicylic Acid on transepidermal water loss (TEWL) was determined (Guillaume et al., 1981). Five mg/cm^2 of 5% Salicylic Acid in an

w/o emulsion was applied once a day for 7days under an occlusive patch to a 5 cm x 5 cm area of the ventral forearm of six male and three female subjects. Untreated open and occluded control sites were used, as was an occluded site with vehicle only. TEWL was measured 1 h after patch removal. The average TEWL was 1.47 mg/cm^2/h and the range was 0.53-3.24 mg/cm^2/h. TEWL was significantly increased by Salicylic Acid compared to both the open and occluded untreated control site and the occluded vehicle site.

In a second study, Guillaume et al. (1981) applied 5% Salicylic Acid in a w/o emulsion in an open manner twice daily for 10 days to the ventral forearm of eight male and four female subjects. TEWL was measured 1 h after the last application. An untreated and vehicle control site were used. The average TEWL was 0.63 mg/cm^2/h and the range was 0.37-1.05 mg/cm^2/h. TEWL was significantly increased by Salicylic Acid compared to both the untreated and vehicle control sites.

The keratoplastic effect of Salicylic Acid was examined using the cantharidin blister model (Gloor and Beier, 1984). Salicylic Acid, 6% in a 70% isopropyl alcohol solution, was applied to the right lower inner arm of seven male subjects twice daily for 10 days. Isopropyl alcohol only was applied to the left arm, which served as a control. After the last dose on day 10, a 0.1% cantharidin solution in acetone was applied to both arms, the subepidermal blister which formed was removed, and the number of cell layers in the corneal layer was examined. The number of cell layers was significantly less from the test site than the control site, indicating that Salicylic Acid had a keratoplastic effect.

The effect of Salicylic Acid on corneocyte surface area was determined using 10 male subjects with normal skin (Robinson et al., 1994). Salicylic Acid, 5% in an alcoholic gel, was applied to a 12 x 6 cm area of the back of each subject six days per wk for 4 wks. The vehicle, 2.5% w/w hydroxypropylcellulose, 0.05% w/w butylhydroxytoluene, and ethyl alcohol, was also applied, and an untreated site was used as a control site. The subjects were to avoid exposing the test sites to sunlight. Corneocyte samples were taken prior to dosing and on study days 7, 14, 21, and 29, and surface area measurements were performed using image analysis. Dermatitis, characterized by desquamation with minimal or no erythema and by pruritus, was observed as of wk 1. No significant differences were observed between treated and control site corneocytes. At all test sites, cyclical changes in mean surface area with respect to baseline were observed.

A tape-stripping technique was used to determine the keratolytic potential of Salicylic Acid (Lodén et al., 1995). Fifty ml of 0.5 and 2.0% Salicylic Acid in an aq. vehicle containing 30% ethyl alcohol were applied to the skin of the inner upper arm of 10 subjects using Finn chambers. At 3 and 6 h after application, the chambers were removed and the test sites were tape stripped six times. The transmission of light through the tape was measured with a digital light measuring instrument.

The authors reported that significantly more material was detached from the site treated with 2% Salicylic Acid for 6 h than was detached from vehicle-treated skin, especially seen at the third and fourth tape stripping; however, less material was removed from the Salicylic Acid-treated area at the first tape stripping as compared to the area treated with vehicle only. The researchers also examined the absorption of Salicylic Acid *in vitro* by tape stripping human breast skin that was exposed to 0.5 and 2.0% Salicylic Acid for 3 and 6 h. Five to 18 µg/cm^2 was found in the tape strips; greater amounts were found with 2% Salicylic Acid, especially at the 3 h stripping.

Six subjects were used in a study examining the effect of Salicylic Acid on the skin (Piérard et al., 1997). Salicylic Acid, 5% in a nonionic o/w vehicle, was applied to the forearm of each subject twice daily for 4 wks. Vehicle alone was also applied, and a non-treated control site was used. The dermal effects were determined using immunohistochemistry and computerized image analysis. Changes in epidermal renewal, modifications in cytokeratin and filaggrin patterns, and TNF-α were examined. Both the Salicylic Acid- and vehicle-treated sites were similar to the untreated control site.

THERAPEUTIC ACTION

Salicylic Acid

Fourteen patients, 11 males and three females, with various forms of ichthyosiform dermatoses were used to evaluate the therapeutic potential of more than 60 chemicals, including Salicylic Acid

(Van Scott and Yu, 1974). Salicylic Acid was dissolved in either water or ethanol and incorporated into a hydrophilic ointment of plain petrolatum. The ointment, containing 10% Salicylic Acid (pH not specified), was applied twice daily to the appropriate test site for 2 wks. Daily to weekly observations were made. Salicylic Acid provided 1+ improvement [slight improvement over that provided by vehicle alone].

A study investigating the effect of Salicylic Acid on treatment of psoriasis was completed with patients with chronic stable plaque-type psoriasis covering greater than 10% of the skin (Kristensen and Kristensen, 1991). The patients had skin types II-IV, and emollient to which 2% Salicylic Acid had been added was used. The patients were irradiated three to five times weekly for up to 6 wks using UV cabins equipped with 16 Philips TL 12 lamps that gave an output of 1.35 mW/cm^2. Maximum irradiation time was 15 min, giving 1.215 J/cm^2. Salicylic Acid decreased clearing in eight of the 11 patients (73%) treated with the Salicylic Acid emollient. These results were significant compared to patients treated without Salicylic Acid.

THERAPEUTIC TOXICITY

A retrospective study involving seven clinicians examined whether hepatomegaly was associated with salicylate therapy in the management of juvenile rheumatoid arthritis (Abbott and Harrisson, no date). A total of 218 cases were reviewed with salicylate dosages of up to 4800 mg/day for 8-10 yrs. No link between salicylate therapy and hepatomegaly was found. These same authors examined possible changes in the density of metaphyses in affected joints due to salicylate administration (Abbott and Harrisson, no date). X-rays from a combined total of 155 cases were reviewed in which various forms of salicylates were administered at doses of 100-3240 mg for several mos to intermittent dosage for 14 yrs. No bone lesions were seen.

Salicylic Acid

Signs and symptoms of Salicylic Acid poisoning include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, possible skin eruptions (Sax, 1979), lethargy, hyperventilation, tachycardia, and fever (Klein-Schwartz, 1983). Severe poisoning can result in delirium, hallucinations, convulsions or coma, and respiratory or cardiovascular collapse. Patients allergic to salicylates have had urticarial, anaphylactic, and erythema multiforme reactions (Goldsmith, 1979). "Significant" salicylate concentrations can affect platelet function and alter blood coagulation. Blood concentrations of salicylate that are >2.17 mM (300 µg/ml) are considered toxic (Moore et al., 1995). Birmingham et al. (1979) stated that serum salicylate concentrations >20 mg/dl can cause toxic symptoms. The adverse effects of aspirin, especially gastric irritation and bleeding, are due to Salicylic Acid (Salako et al., 1989).

Toxic reactions to salicylate generally occur more frequently in children because their extracellular fluid volume is small in comparison to the potential areas of application (Taylor and Halprin, 1975). With the elderly, care must be taken in prescribing salicylate-containing drugs (and/or other drugs); systemic clearance of salicylates (mainly by hepatic metabolism) may be reduced with age (Dumas and Cusack, 1992).

Methyl Salicylate

Methyl Salicylate taken in quantities of ≥1 tsp are reported to be "quite toxic" (21 CFR 201.303). (One tsp (5 ml) Methyl Salicylate is equivalent to 7000 mg salicylate or 21.7 325 mg aspirin tablets.) The oral LD_{Lo} of Methyl Salicylate was 170 mg/kg (Sax, 1979). Accidental acute poisoning is not uncommon, especially in children. Kidney irritation, vomiting, and convulsions occur.

The average lethal dose of Methyl Salicylate is 10 ml for children and 30 ml for adults (Environmental Health Research and Testing, Inc., 1984). Common symptoms of toxicity include nausea, vomiting, acidosis, pulmonary edema, pneumonia, convulsions, and possibly death.

Concomitant use of Methyl Salicylate and drug substances can be problematic. Use of topical analgesic preparations containing Methyl Salicylate in conjunction with oral warfarin can result in adverse reactions and bleeding (Chan, 1996).

Sodium Salicylate

Sodium Salicylate is a "powerful irritant" (Sax, 1979). It can affect the central nervous system.

CASE STUDIES

Numerous case studies documenting the toxic potential of Salicylic Acid, Sodium Salicylate, and Methyl Salicylate have been reported (Troll and Menten, 1945; Ashworth and McKemie, 1944; Ryder et al., 1945; Craig, 1953; Adams et al., 1957; Winek et al., 1973; Pascher, 1978; Lester and Davis, 1984; Howrie et al., 1985; Litovitz and Manoguerra, 1992; Koren, 1993; Liebelt and Shannon, 1993; Chan et al., 1995); these studies involve oral ingestion. Toxicity has also been described with dermal application of salicylates for management of skin diseases in which 3-21% Salicylic Acid was applied (Cawley et al., 1952; von Weiss and Lever, 1964; Lindsey, 1968; Luderschmidt and Plewig, 1975; Davies et al., 1979; Raschke et al., 1991; Abdel-Magid and Ahmed, 1994; Dwyer et al., 1994; Germann et al., 1996; Chiaretti, 1997); in one case study, toxicity was observed as a result of dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug (Shupp and Schroeter, 1986). Additionally, toxicity was observed with an elderly subject recovering from acute renal failure following dermal application of a Salicylic Acid ointment (Smith and Lyons, 1980). Dermal application of a product containing Methyl Salicylate produced toxicity (Bartle et al., 1992), and topical application of Methyl Salicylate (and menthol) followed by the application of heat resulted in skin and muscle necrosis and interstitial nephritis (Heng, 1987). In a patch test of a patient with acute dermatitis who had been using an ointment containing menthol, camphor, and 12% Methyl Salicylate, positive results were seen with 2% Methyl Salicylate in arachis oil and 2% aq. Sodium Salicylate (Hindson, 1977). A case study was reported in which Methyl Salicylate caused severe urticaria and angioedema (Speer, 1979).

In two case studies of reactions to a wart paint containing Salicylic Acid, patch testing showed that Salicylic Acid (tested at 3% in petrolatum) was not the causative agent (Lachapelle and Leroy, 1990). Rudzki and Koslowska reported positive reactions to 5% Salicylic Acid in yellow soft paraffin in four patients with dermatitis and one with psoriasis; the four patients with dermatitis had used a 2% "salicylic spirit", and the one with psoriasis had used a "5% unguentum salicylicum".

SUMMARY

Salicylic Acid is an aromatic acid used in cosmetic formulations as a denaturant, a hair conditioning agent, and a skin conditioning agent - miscellaneous. The Calcium, Magnesium, and MEA salts are used as preservatives. Potassium Salicylate is used as a cosmetic biocide and preservative. Sodium Salicylate is used as a denaturant and preservative. The TEA salt of Salicylic Acid is used as a UV light absorber. Several Salicylic Acid esters are used as skin conditioning agents - miscellaneous (Capryloyl, C12-15 Alkyl, Isocetyl, Isodecyl, and Tridecyl). Butyloctyl Salicylate and Hexyldodecyl Salicylate are used as hair conditioning agents and skin conditioning agents - miscellaneous. Ethylhexyl Salicylate (formerly known as Octyl Salicylate) is used as a fragrance ingredient, sunscreen agent, and UV light absorber, and Methyl Salicylate is used as a denaturant and flavoring agent. Myristyl Salicylate has no reported function.

Salicylic Acid and Methyl Salicylate are soluble in organic solvents, but only slightly soluble in water. Ethylhexyl Salicylate is not soluble in water. Calcium, Potassium, and Sodium Salicylate are soluble in water. Potassium Salicylate is reported to be very soluble in water and alcohol. These ingredients have either no odor or only a faint odor, except for Methyl Salicylate, which has the characteristic odor of wintergreen. Consistent with the several medical treatments involving salicylates, test methodologies have been developed for detecting Salicylic Acid in urine and serum. Heavy metal concentration limitations are described for USP grade Magnesium, Sodium and Methyl Salicylate and for cosmetic grade Methyl Salicylate. Salicylic Acid and Ethylhexyl Salicylate absorb UVB radiation.

Salicylic Acid is used in 107 cosmetic formulations at concentrations ranging from 0.0008% to 3%. Ethylhexyl Salicylate is used in 87 formulations at 0.001% to 8%. Methyl Salicylate is used in 25 formulations at 0.0001% to 0.6%. Sodium Salicylate is used in 7 formulations at 0.09% to 2%. TEA-Salicylate is used in 5 formulations at 0.0001% to 0.75%. Capryloyl Salicylate is used in 5 formulations at 0.1% to 1%. Isodecyl Salicylate is used in 3 formulations, but no concentration of use information was reported. Isocetyl Salicylate is not reported to FDA as used, but is reported to CTFA as being used at concentrations ranging

from 3% to 5%. Likewise, Butyloctyl Salicylate is not reported to FDA as being used, but is reported to CTFA as being used at 0.5% to 5%. Methyl Salicylate is used in perfumery.

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate are allowed for use in cosmetics in the European Union as preservatives at a maximum concentration of 5% (acid), except that these ingredients are not to be used in preparations for children under 3 yrs of age, except for shampoo formulations, which must bear a label warning against use on children under 3 yrs of age.

In Japan, Salicylic Acid which conforms to the standards of the *Japanese Standards of Cosmetic Ingredients (JSCI)* has precedent for use at a maximum concentration of 0.2% in all categories except eyeliner preparations, in which it is not used. Sodium Salicylate which conforms to the specifications of the *JSCI* has precedent for use at a maximum concentration (calculated as total Salicylic Acid) of 1% in cleansing preparations and of 0.2% in hair care, treatment, makeup, fragrance, suntan and sunscreen, and nail makeup preparations; it is not used in eyeliner, lip, oral, or bath preparations. Sodium Salicylate is restricted as to the per cent as total Salicylic Acid salts allowed in a formulation. Methyl Salicylate which conforms to the specifications of the *JSCI* has precedent for use at a maximum concentration of 0.1% in all CLS categories except eyeliner preparations, in which it is not used. Ethylhexyl Salicylate which conforms to the specifications of the *Japanese Cosmetic Ingredient Codex* has precedent at a maximum concentration of 10% in suntan/sunscreen preparations and of 1% in all other CLS preparations except eyeliner and bath preparations, in which it is not used. Methyl and Ethylhexyl Salicylate are restricted in that the total percentage of UV absorbers in a formulation shall not exceed 10%.

These ingredients have uses in foods and drugs that are regulated by FDA. Salicylic Acid, Magnesium Salicylate, Sodium Salicylate, and Methyl Salicylate have FDA specified uses as indirect food additives. Salicylic Acid is an approved active ingredient for use in topical over-the-counter (OTC) acne drug products at concentrations of 0.5-2%, in OTC wart remover drug products at concentrations of 12-40% in a plaster vehicle, 5-17% in a collodion-like vehicle, and 15% in a karaya gum, glycol plaster vehicle, with proper labeling directions, in corn and callus remover OTC drug products at concentrations of 12-40% in a plaster vehicle and 12-17.6% in a collodion-like vehicle with proper labeling directions, and in OTC drugs for the control of dandruff, seborrheic dermatitis, and psoriasis at a concentration of 1.8-3%.

Salicylic Acid has been present in OTC topical acne preparations (at concentrations of 2-5%), external analgesics and skin protectants used for poison ivy, oak, and sumac, and topical antifungal drug products; Calcium Salicylate has been present in OTC internal analgesic drug products; Sodium Salicylate has been present in OTC dandruff/seborrheic dermatitis/psoriasis and digestive aid drug products; TEA-Salicylate has been present in OTC external analgesic - fever blister and cold sore, - insect bite and sting, and - poison ivy, oak, and sumac drug products; Methyl Salicylate has been present in OTC smoking deterrent drugs, boil treatment, dandruff/seborrheic dermatitis/psoriasis, fever blister and cold sore treatment, oral health care, and skin protectant - astringent drug products; however, currently FDA has concluded that there is inadequate data to establish general recognition of the safety and effectiveness of these ingredients for these specified OTC uses.

Any drug product intended to be taken orally that contains any salicylate ingredient, except effervescent preparations, must bear a statement warning to keep the product out of the reach of children. Any drug containing >5% Methyl Salicylate must bear a label that warns that misdirected use may be dangerous and that the product should be kept out of the reach of children. TEA-Salicylate is allowed for use as an active ingredient in sunscreens at concentrations of <12%, while Ethylhexyl Salicylate is allowed at concentrations of <5%.

In veterinary practice, Salicylic Acid is allowed for use in the removal of scar tissue from the teat canal of milk-producing cows; however, a residue tolerance of 0 has been established for milk from dairy animals.

In the medical literature, Salicylic Acid has been used in the treatment of ichthyosiform dermatoses. A traditional use of Methyl Salicylate is as a counterirritant.

Salicylic Acid is used in the manufacture of aspirin. Salicylic Acid is also used in the manufacture of salicylates and resins and as a dyestuff intermediate, prevulcanization inhibitor, analytical reagent, and fungicide. Sodium Salicylate is used as a preservative for paste, mucilage, glues, and hides.

Absorption of salicylates from the stomach is normally rapid. Extensive data are available in animals and humans from oral delivery studies. Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids. Salicylates are also absorbed percutaneously. Urinary metabolites resulting from percutaneous delivery are reportedly quantitatively different from those seen with oral delivery, with more glucuronides found and more unmetabolized Salicylic Acid. Data on percutaneous absorption are available from *in vitro* and *in vivo* testing of penetration through animal skin. *In vitro* data are available for pig, mouse, and rat skin. *In vivo* percutaneous absorption data are available for rabbits, guinea pigs, rats, mice (including hairless mice), dogs, and monkeys. Data describing penetration through human skin are also available. These animal and human data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol>water); absorption varies as a function of pH; and absorption is greater through damaged skin compared to normal skin. Around 10% of applied salicylates can remain in the skin. Parenteral absorption data are also available.

Salicylic Acid is keratolytic. Salicylic Acid is reported to enhance percutaneous penetration of vitamin A, ammoniated mercury, and triamcinolone acetonide, but not methyl nicotinate (which itself rapidly penetrates skin), hydrocortisone, diflucortolone-21-valerate, or cyclosporin.

Reversable hearing loss and tinnitus is a reported side-effect of salicylates at therapeutic levels.

One study describes the minimal inhibitory concentrations of Salicylic Acid against bacteria, yeasts, and fungi, asserting that its preservative action is restricted to the pH range 2-5. Other data show that Salicylic acid inhibits growth of the following cells in culture: HeLa, human prostatic carcinoma, dog distal renal tubular, pig renal proximal tubular, rat kidney, human hepatoma, *B. subtilis*, and *E. coli*. Sodium Salicylate inhibits growth of human fibroblast and rat hepatoma cells in culture at high doses. Inhibition of inducible nitric oxide synthetase is one hypothesis for the cytotoxicity of Sodium Salicylate in several mammalian cell lines. Methyl Salicylate inhibited HeLa and *B. subtilis* cell growth in culture.

Salicylic Acid has anti-inflammatory effects. Sodium Salicylate influences interferon titres in mice; interferes with neutrophil function *in vitro*; inhibits induction of chemokine mRNA and activation of nuclear factor-κB in bone marrow cells; inhibits TNF-induced activation of c-Jun N-terminal kinase and c-fos mRNA in human diploid fibroblasts; and enhances tyrosine phosphorylation and increases p38 kinase activity in COS cells. Methyl Salicylate produced an inflammatory response in the ear of female mice, but *in vitro* exposure of human epidermal keratinocytes to Methyl Salicylate failed to induce IL-8, TNF-α, or granulocyte/macrophage colony-stimulating factor.

Salicylic acid produces pharmacologic/physiologic effects as follows: increases the stability of lysosomal membranes in rats and decreases alanine aminotransferase activity in the medium of cultured rat hepatocytes. Sodium Salicylate influenced blood pH in rats, and markedly increased bile flow in rats dosed i.p., but few other hepatic changes were seen.

Little acute toxicity (LD_{50} in rats; >2 g/kg) via a dermal exposure route is seen for Salicylic Acid, Methyl Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. These compare with oral acute LD_{50} values for Salicylic Acid in rats ranging from a low of 0.891 g/kg to a high of 1.58 g/kg; for Sodium Salicylate, between 0.9 g/kg and 1.7 g/kg; for Isodecyl Salicylate, no toxicity at levels as high as 4.83 g/kg; for Methyl Salicylate, between 0.887 g/kg and 1.25 g/kg; for Ethylhexyl (Octyl) Salicylate, >2 g/kg; for Tridecyl Salicylate, >1.98 g/kg; and for Butyloctyl Salicylate, >5 g/kg. Values for acute oral toxicity in other species are consistent with these values. Methyl Salicylate given by inhalation is not lethal in mice and rats. The parenteral LD_{50} for Salicylic Acid in mice is 0.52 g/kg and the acute toxicity of Sodium Salicylate Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, and Tridecyl Salicylate via this route of administration are

generally in the one gram per kilogram range.

Short-term oral, inhalation, and parenteral exposures to Methyl Salicylate are available. Inconsistent results are seen regarding bone lesions with oral exposures, but reduced growth and feed consumption are consistently seen. No toxicity is seen with inhalation of Methyl Salicylate in a series of 20 exposures of 7 h each at 0.7 g/m^3 and no bone lesions were seen with parenteral exposure. Sodium Salicylate oral exposures are linked with reduced growth and feed consumption, clear kidney damage, and some liver damage; parenteral exposures result in hyperpnea and profuse diuresis in single animal experiments. Salicylic Acid oral delivery produces liver and plasma enzyme changes.

Subchronic dermal, oral, and inhalation studies are available for Methyl Salicylate. Dermal and inhalation exposures are associated with kidney damage. Inhalation exposures also produce pulmonary focal hemorrhages and hyperplasia. Oral exposure results in reduced weight gain and bone lesions which disappear if Methyl Salicylate is coadministered with Calcium Carbonate. No toxicity is seen with oral subchronic exposure to Isodecyl Salicylate or Tridecyl Salicylate. Oral subchronic exposure to Sodium Salicylate is associated with reduced growth and feed consumption, and indication of some bone lesions and isolated muscle weakness.

Chronic exposure data are available for Methyl Salicylate. Adverse effects are seen as a function of the level of exposure in 2 yr rat studies, with 2% producing bone lesions and 0.7% not doing so. Liver damage is seen in dogs exposed to 0.15 g/kg/d in one study, kidney and liver weight increases in another study at the same exposure, but no liver or kidney abnormalities in a study at 0.167 g/kg/d.

Dermal irritation studies are available for Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. Application of 500 mg (in 0.5 ml) of Isodecyl, Tridecyl, and Butyloctyl Salicylate are not irritating. Undiluted application of Ethylhexyl (Octyl) Salicylate produces minimal to mild irritation. Methyl Salicylate at concentrations of greater than 50% is clearly irritating. One study of the effect of vehicle on Methyl Salicylate irritation shows irritation at concentrations as low as 1% with a 70% ethanol vehicle producing the most irritation and polyethylene glycol producing little or no irritation at Methyl Salicylate concentrations up to 6%.

The ocular irritation potential is negative for Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate.

Data are available on the use of a local lymph node assay to determine the sensitization potential of Salicylic Acid and Methyl Salicylate. While Salicylic Acid at a concentration of 20% in acetone is positive in this assay, a concentration of 20% in acetone/olive oil is not. Methyl Salicylate is negative at concentrations up to 25%, independent of vehicle. Maximization tests of Methyl Salicylate are negative, as they are for Ethylhexyl (Octyl) Salicylate and Butyloctyl Salicylate. Neither Salicylic Acid nor Tridecyl Salicylate are photosensitizers.

Salicylic Acid, produced when aspirin is rapidly hydrolyzed to Salicylic Acid after absorption from the gut, was reported to be the causative agent in aspirin teratogenesis in animals. Dermal exposures to Methyl Salicylate, oral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate, and parenteral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate are all associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure.

An exposure assessment of a representative cosmetic product used on a daily basis is available which estimates that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. This exposure assessment further contends that the reproductive and developmental toxicity from the daily use of a baby aspirin is not significant.

Studies of the genotoxic potential of Salicylic Acid, Sodium Salicylate, Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate are negative, except that Salicylic Acid is positive in a *B. subtilis* rec-assay (negative in 7 other bacterial tests and one mammalian test); Methyl Salicylate is positive in *S. typhimurium* strains TA98 and TA100 with metabolic activation (negative in two other Ames tests); and Sodium Salicylate is positive in an *in vivo* chromosome aberration study in mice (negative sister chromatid

exchange *in vivo* in mice, and in four *in vitro* test systems).

Methyl Salicylate, in a mouse skin painting study, does not induce neoplasms. Likewise, Methyl Salicylate is negative in a mouse pulmonary tumor system. *In vitro* predictors of carcinogenesis are also negative for Salicylic Acid and Sodium Salicylate.

Clinical tests for cumulative irritation are available for the following ingredients at the specified concentrations: Salicylic Acid (2% - minimal cumulative irritation, 1.5% slight or no irritation); TEA-Salicylate (8% - no irritation); Methyl Salicylate (>12% - pain and erythema, 8%, - no irritation, 1% aerosol - erythema); Ethylhexyl (Octyl) Salicylate (4% - no irritation); and Tridecyl Salicylate (no irritation). In 20 patients with eczema or contact dermatitis, Methyl Salicylate at 67% is reported to cause irritation in 8 subjects; at 40% - 2 subjects; and at 38%, 15%, and 3.75% - no irritation in any subject.

If Salicylic Acid is applied after the application of agents (benzoic acid, cinnamic aldehyde, methyl nicotinate, and DMSO)known to cause non-immunologic immediate contact reactions in the skin, the erythema induced by benzoic acid, cinnamic aldehyde, and methyl nicotinate is reduced, but there is no effect on edema.

In normal skin, Salicylic Acid, Methyl Salicylate, and Ethylhexyl (Octyl) Salicylate are not sensitizers. In patients with venous leg eczema, Salicylic Acid augments histidine release in 3/320 challenged with ragweed pollen. Sodium Salicylate injected in the skin of aspirin intolerant individuals affected several parameters as follows: 1/23 had a positive skin test to Sodium Salicylate; 2/31 were positive in the passive cutaneous anaphalaxis test; and 2/26 were positive in the lymphocyte transformation test. Salicylic Acid is not a photosensitizer, nor is it phototoxic. Salicylic Acid and Ethylhexyl (Octyl) Salicylate are low level photoprotective agents.

Salicylic Acid exacerbates urticarial reactions to aspirin; 13 of 18 patients in one study and six of 20 in another. At 5% in petrolatum, however, Salicylic Acid does not cause any urticarial reactions in atopic, urticarial, non-atopic, and non-allergic patients.

Salicylic Acid is well-documented to have keratolytic action on normal human skin. It had a small therapeutic effect in patients with various forms of ichthyosiform dermatoses, but decreased clearing in 8 of 11 psoriasis patients when compared to UV therapy alone. Therapeutic toxicities include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, skin eruptions, and fever. One estimate is that a blood concentration >300 µg/ml of a salicylate should be considered toxic. Toxic reactions occur more frequently in children. Care must be taken in prescribing salicylate-containing medications because systemic clearance of salicylates may be reduced with age. Severe poisoning can result in delirium, hallucinations, convulsions, coma, and respiratory or cardiovascular collapse.

Methyl Salicylate taken in quantities greater than or equal to 1 tsp are reported to be quite toxic (equivalent of the salicylate that could be derived from 20+ adult aspirin tablets). Accidental poisoning is not uncommon, especially in children; symptions of poisoning include kidney irritation, vomiting, and convulsions. The average lethal dose of Methyl Salicylate is 10 ml for children and 30 ml for adults. Use of topical analgesics with Methyl Salicylate in combination with oral warfarin can result in adverse reactions.

Numerous case studies reporting toxic reactions to oral ingestion of salicylates. Dermal toxicity is also described in the case literature as follows: - dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug; following dermal application of a Salicylic Acid ointment in an elderly subject recovering from acute renal failure; topical application of Methyl Salicylate (and menthol) followed by the application of heat (skin and muscle necrosis and interstitial nephritis); and severe urticaria and angioedema with Methyl Salicylate exposure.

In two case studies of reactions to a wart paint containing Salicylic Acid, Salicylic Acid (tested at 3% in petrolatum) was not the causative agent. Two percent Methyl Salicylate in arachis oil and 2% aq. Sodium Salicylate produced positive positive patch test results in a patient with acute dermatitis who had been using an ointment containing menthol, camphor. Twelve percent Methyl Salicylate and 5% Salicylic Acid in yellow soft paraffin produced positive patch tests in four patients with dermatitis and one with psoriasis, all with some history of exposure to salicylates.

A review of radiographs taken in 155 cases of juvenile arthritis in which various forms of salicylates had been administered at concentrations ranging from 0.1 to 3.24 g for several months did not find any evidence of bone lesions.

DISCUSSION

The CIR Expert Panel considered that the available information is sufficient to evaluate the safety of these ingredients in cosmetic formulations. In reaching its conclusion, the Panel considered three primary issues: 1) increased sun sensitivity (e.g., ultraviolet radiation induced skin damage); 2) skin irritation; and 3) reproductive and developmental toxicity.

The Panel expects that these ingredients will have application as exfoliating agents in cosmetic formultations at concentrations of use at the high end of the currently reported use levels, in addition to the other uses that have been specified. In that regard, the Panel expressed concern that repeated use of Salicylic Acid and the various salicylates may effectively increase exposure of the dermis and epidermis to ultraviolet radiation. On the other hand, information is available suggesting that these ingredients absorb ultraviolet radiation, which would decrease the exposure. Data are not available that suggest what the balance of these two influences would be vis a vis ultraviolet radiation induced skin damage. Drawing on its previous experience in reviewing the safety of alpha hydroxy acids (AHAs), the Panel compared the relatively mild exfoliating action of Salicylic Acid and the various salicylates with that of AHAs, factored in the ultraviolet radiation absorption by salicylates, and estimated that the small increase in sun sensitivity associated with use of AHAs would likely be smaller still with salicylates.

The Panel considered requesting additional safety testing of these ingredients to resolve this question of the existence and/or magnitude of an increase in sun sensitivity, but was convinced that the exfolient action alone would always raise the possibility that some increase in ultraviolet radiation induced skin damage would be detected, e.g. if more animals had been used, if a more sensitive assay for damage were available, etc. Were there to be evidence of a small increase in sun sensitivity associated with the use of Salicylic Acid and the several salicylates at exfolient concentrations, or were the available data to be equivocal, the Panel reasoned that the appropriate conclusion would be that these ingredients could be used safely as exfoliants, if expressly formulated to avoid increasing a user's sun sensitivity. Accordingly, the Panel concluded that the prudent course of action would be to advise the cosmetics industry that there can be a risk of increased ultraviolet radiation damage with the use of any exfoliant, including Salicylic Acid and the listed salicylates, and that steps need to be taken to formulate cosmetic products with these ingredients as exfoliating agents so as not to increase sun sensitivity, or when increased sun sensitivity would be expected, to include directions for the daily use of sun protection.

The Panel was concerned that the available data were not sufficient to establish a limit on concentration of these ingredients, or to identify the minimum pH of formulations containing these ingredients, such that no skin irritation would occur. Such limits were established with AHAs. Because the available animal and clinical safety test data demonstrate that these ingredients are generally milder than AHAs, the Panel was convinced that it is possible to formulate cosmetic products in a way such that significant irritation would not be likely. Therefore, the Panel concluded that the cosmetics industry should formulate products containing these ingredients so as to be non-irritating.

Reproductive and developmental toxicity associated with exposures to large, therapeutic serum concentrations of Salicylic Acid (as a metabolite of aspirin) have been extensively demonstrated. The Panel considered the possibility that use of Salicylic Acid or the various salicylates could produce serum levels of Salicylic Acid or, with other sources (e.g., aspirin), contribute to serum levels and thereby present a reproductive and developmental toxicity risk. Beginning with the premise that ingestion of a low-dose regimen (81 mg) aspirin by a 58 kg female would result in an exposure of ~1.4 mg/kg/day and that this exposure level is not considered to present any reproductive or developmental toxicity risk, the Panel considered that a representative exposure to a cosmetic product containing Salicylic Acid could result in exposure to ~0.4-0.5 mg/kg/day and would not present a risk. While simultaneous use of several products containing Salicylic Acid could produce exposures greater than would be seen with a baby

aspirin, the Panel also did not consider it likely that consumers would simultaneously use multiple cosmetic products containing Salicylic Acid. Thus, the serum levels of Salicylic Acid that would result from dermal application would likely be less than serum levels from ingestion.

CONCLUSION

Based on the available information, the CIR Expert Panel concluded that Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate, the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

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REFERENCES

Abbott D.D. and Harrisson, J.W.E.. (No date) Methyl Salicylate: Studies of osseous changes in the rat, reproduction in the rat and mouse, and liver and kidney effects in the dog. (Submitted by the Food and Drug Administration (FDA) in response to a Freedom of Information (FOI) request - 1998; 65 pp.)[1]

Abdallah, H.Y., M. Mayersohn, and K.A. Conrad. 1991. The influence of age on salicylate pharmacokinetics in humans. *J Clin Pharmacol* 31(4):380-7.

Abdel-Magid, E.H. and F.-R.E.A. Ahmed. 1994. Salicylate intoxication in an infant with ichthyosis transmitted through skin ointment -- A case report. *Pediatrics* 94:939-40.

Abramson, S.B., J. Leszczynska-Piziak, K. Haines, and J. Reibman. 1991. Non-steroidal anti-inflammatory drugs: Effects on a GTP binding protein within the neutrophil plasma membrane. *Biochem Pharmacol* 41(11):1567-73.

Adams ,J.T., J.A. Bigler, and O.C. Green. 1957. A case of methyl salicylate intoxication treated by exchange transfusion. *J Am Med Assoc* 165(12):1563-5.

Akita, M., A. Yokoyama, and Y. Kuroda. 1995. The study of salicylate-induced cleft lip on cultured rat embryos. Abstract P-54. *Teratology* 52(4):43B.

[1]Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, D.C. 20036.

Alam, A.S., D. Gregoriades, and A.R. Imondi. 1981. Bioavailability of magnesium salicylate. *J Pharm Pharmacol* 33(12):792-3.

Allen, J.M., C.J. Gossett, and S.K. Allen. 1996. Photochemical formation of singlet molecular oxygen in illuminated aqueous solutions of several commercially available sunscreen active ingredients. *Chem Res Toxicol* 9(3): 605-9.

Alpen, E.L., H.G. Mandel, V.W. Rodwell, and P.K. Smith. 1951. The metabolism of C^{14} carboxyl salicylic acid in the dog and in man. *J Pharmacol Exp Ther* 102:150-5.

Amin, A.R., P. Vyas, M. Attur, et al. 1995. The mode of action of aspirin-like drugs: Effect on inducible nitric oxide synthase. *Proc Natl Acad Sci USA* 92(17):7926-30.

Andrews, H.B. 1973. Salicylate poisoning. *Am Fam Physician* 8(5):102-6.

Anonymous. 1976. Fragrance raw materials monographs: Ethyl Hexyl Salicylate. *Fd Cosmet Toxicol* 14:765.

Arita, T., R. Hori, T. Anmo, et al. 1970. Studies on percutaneous absorption of durgs. *Chem Pharm Bull* 18(5):1045-9.

Arts, J.H.E., S.C.M Droge, S. Spanhaak, et al. 1997. Local lymph node activation and IgE responses in Brown Norway and Wistar rats after dermal application of sensitizing and non-sensitizing chemicals. *Toxicology* 117 (2-3):229-37.

Ashworth, C.T. and J.F. McKemie. 1944. Hemorrhagic complications with death probably from salicylate therapy. Report of two cases. *J Am Med Assoc* 126:806-10.

Babar, A., P.J. Chickhale, and F.M. Plakogiannis. 1991. Assessment of triethanolamine salicylate release from the dermatological bases and the commercial products. *Pharm Acta Helv* 66(12):322-8.

Baldwin, J.R., R.A. Carrano, and A.R. Imondi. 1984 Penetration of trolamine salicylate into the skeletal muscle of the pig. *J Pharm Sci* 73(7):1002-4.

Barbour, H.G. and M.E. Fisk. 1933. Liver damage in dogs and rats after repeated oral administration of cinchophen, ethyl ester of paramethyl-phenylcinchoninic acid (tolysin) and sodium salicylate. *J Pharmacol Exp Ther* 48:341-57.

Bartle, B., P. Morra, S. Walker, and S. Bowles. 1992. Salicylate toxicity -- from topical methylsalicylate. *On Contin Pract* 19(2):23-5.

Basketter, D.A. and E.W. Scholes. 1992. Comparison of the local lymph node assay with the guinea pig maximization test for the detection of a range of contact allergens. *Fd Chem Toxicol* 30(1):65-9.

Basketter, D.A., E.W. Scholes, and I. Kimber. 1994 The performance of the local lymph node assay with chemicals identified as contact allergens in the human maximization test. *Fd Chem Toxicol* 32(6):543-7.

Bekemeier, H. 1955. Salicylamide acid and salicylic acid intoxication in cats, compared with other animals. *Arznei, Forsch* 5:572-5.

Benfeldt, E., J. Serup, and T. Menné. 1999. Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: *In vivo* pharmacokinetics using microdialysis and non-invasive quantification of barrier function. *Br J Dermatol* 140:739-48.

Bergman, K., E. Cekan, P. Slanina, J. Gabrielsson, and K.-E. Hellenas. 1990. Effects of dietary sodium selenite supplementation on salicylate-induced embryo- and fetotoxicity in the rat. *Toxicology* 61(2):135-46.

Beutner, R., B. Calesnick, E. Powell, and L. Bortin. 1943. Clinical and Experimental: On the absorption and excretion of methylsalicylate administered by inunction. *J Lab Clin Med* 28(14):1655-63.

Beyer, P.E. and N. Chernoff. 1986. The induction of supernumerary ribs in rodents: Role of the maternal stress. *Teratog Carcinog Mutagen* 6(5):419-29.

Beyer, B.K. and W.F. Geber. (1984) Fetal lateral cerebral ventricular enlargement induced by exposure to selected teratogenic agents. Abst 331 *Toxicologist* 4:83.

Biolab. 1997a. *Salmonella typhimurium* reverse mutation assay. Study 96/1636.A2 dated Mar 5. Unpublished data submitted by CTFA. 15 pp.[1]

Biolab. 1997b. Skin irritation in man of Tridecyl Salicylate. Patch test according to Draize modified. (48 hours occlusive test.) Project no. 96/1636.A1 dated Apr 2. Unpublished data submitted by CTFA. 14 pp.[1]

Biolab. 1998a. Acute dermal toxicity of Tridecyl Salicylate (limit test). Project no. 97/1566.A dated Jan 28. Unpublished data submitted by CTFA. 23 pp.

Biolab. 1998b. Phototoxicity of Tridecyl Salicylate. Project no. 97/1566.A dated Jan 28. Unpublished data submitted by CTFA. 11 pp.[1]

Biolab. 1998c. Acute eye irritation of Tridecyl Salicylate. Contract no. 97/1566.A dated Jan 28. Unpublished data submitted by CTFA. 12 pp.[1]

Birmingham, B.K., D.S. Greene, and C.T. Rhodes. 1979. Systemic absorption of topical salicylic acid. *Int J Dermatol* 18(3):228-31.

Boehnlein, J., A. Sakr, J.L. Lichtin, and R.L. Bronaugh. 1994. Characterization of esterase and alcohol dehydrogenase activity in skin. Metabolism of retinyl palmitate to retinol (vitamin A) during percutaneous absorption. *Pharm Res* 11(8): 1155-9.

Bomhard, E. 1996. Acute toxicity data. Acute toxicological evaluation of Salicylic Acid. *J Am Coll Toxicol* 15(Suppl 1):S81.

Borel, J.F. 1976. Comparative study of *in vitro* and *in vivo* drug effects on cell-mediated cytotoxicity. *Immunology* 31(4):631-41.

Boussiquet-Leroux, C., G. Durand-Cavagna, K. Herlin, and D. Holder. 1995. Evaluation of lymphocyte proliferation by immunohistochemistry in the local lymph node assay. *J Appl Toxicol* 15(6):465-75.

Bronaugh, R.L., S.W. Collier, J.E. Storm, and R.F. Stewart. 1989-90. *In vitro* evaluatioin of skin absorption and metabolism. *J Toxicol - Cut&Oc Toxicol* 8(4):453-67.

Bronaugh ,R.L., R.F. Stewart, and J.E. Storm. 1989. Extent of cutaneous metabolism during percutaneous absorption of xenobiotics. *Toxicol Appl Pharmacol* 99(3):534-43.

Bucks, D.A., R.S. Hinz, R. Sarason, H.I. Maibach,and R.H. Guy. 1990. *In vivo* percutaneous absorption of chemicals: A multiple dose study in rhesus monkeys. *Fd Chem Toxicol* 28(2):129-32.

Budavari, S., ed. 1989. *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th edn. Rahway, NJ:Merck & Co, Inc, 893, 961-2, 1217, 1324, 1367-8.

Buelke-Sam, J., C.A. Kimmel, C.J. Nelson, and P.A. Sullivan 1984. Sex and strain differences in the developmental activity profile of rats prenatally exposed to sodium salicylate. *Neurobehav Toxicol Teratol* 6(2):171-5.

Bullock, G.R., V.B. Delaney, B.C. Sawyer, and T.F. Slater. 1970. Biochemical and structural changes in rat liver resulting from the parenteral administration of a large dose of sodium salicylate. *Biochem Pharmacol* 19:245-53.

Burdette, W.J. and L.C. Strong. 1941. Comparison of methyl salicylate and benzene as solvents for methylcholanthrene. *Cancer Res* 1:939-41.

Caslavska, J., S. Lienhard, and W. Thormann. 1993. Comparative use of three electrokinetic capillary methods for the determination of drugs in body fluids. Prospects for rapid determination of intoxications. *J Chromatogr* 638(2):335-42.

Cawley, E.P., N.T. Peterson, and C.E. Wheeler. 1952. Salicylic acid poisoning in dermatologic therapy. *J Am Med Assoc* 151:372-4.

Cekanova, E., K.S. Larsson, E. Mörck, and G. Åberg. 1974. Interactions between salicylic acid and pyridyl-3-methanol: Anti-inflammatory and teratogenic effects. *Acta Pharmacol Toxicol* 35:107-18.

Chan, T.Y. 1996. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 15(9):747-50.

Chan, T.H., K.C. Wong, and J.C.N. Chan. 1995. Severe salicylate poisoning associated with the intake of Chinese medicinal oil ('Red Flower Oil'). *Aust NZ J Med* 25:57.

Chernoff, N. and R.J. Kavlock. 1982. An *in vivo* teratology screen utilizing pregnant mice. *J Toxicol Environ Health* 10:541-50.

Chernoff, N. and R.J. Kavlock. 1983. A teratology test system which utilizes postnatal growth and viability in the mouse. *Short-Term Bioassays in the Analysis of Complex Environmental Mixtures III, Environmental Science Research* 27:417-27.

Chiaretti, A., D. Schembri Wismayer, L. Tortorolo, M. Piastra, and G. Polidori. 1997. Salicylate intoxication using a skin ointment. *Acta Pædiatr* 86(3):330-1.

Collins, T.F.X., W.H. Hansen, and H.V. Keeler. 1971. Effect of methyl salicylate on rat reproduction. *Toxicol Appl Pharmacol* 18(4):755-65.

Collins, A.J., L.J. Notarianni, E.F.J. Ring, and M.P. Seed. 1984. Some observations on the pharmacology of 'deep heat', a topical rubifacient. *Ann Rheum Dis* 43(3):411-5.

Commoner, B. 1976. Reliability of bacterial mutagenesis techniques to distinguish carcinogenic and noncarcinogenic chemicals. Contract No. 68-01-2471. National Technical Information Service (NTIS) Report No. PB259934.

Cooper, E.R. 1984. Increased skin permeability for lipophilic molecules. *J Pharm Sci* 73(8):1153-6.

Corby, D.G. 1978. Aspirin in pregnancy: Maternal and fetal effects. *Pediatrics* 62(Suppl 5):930-7.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1999. Concentration of use data on Salicylic Acid, Sodium Salicylate, TEA-Salicylate, Capryloyl Salicylic Acid, Isocetyl Salicylate, Methyl Salicylate, Octyl Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. Updated July 12. Unpublished data submitted by CTFA.[1]

CTFA Database. 1999. Function of Capryloyl Salicylic Acid in cosmetics. Unpublished data submitted by CTFA. 1 p.[1]

Coudray, C., C. Mangournet, S. Bouhadjeb, H. Faure, and A. Favier. 1996. Rapid high-performance liquid chromatographic assay for salicylic acid in plasma without solvent extraction. *J Chromatogr Sci* 34(4):166-73.

Craig, J.O. 1953. Poisoning by the volatile oils in childhood. *Arch Dis Child* 28:475-83.

Cronstein, B.N., M. Van de Stouwe, L. Druska, R.I. Levin, and G. Weissmann. 1994. Nonsteroidal antiinflammatory agents inhibit stimulated neutrophil adhesion to endothelium: Adenosine dependent and independent mechanisms. *Inflammation* 18(3):323-5.

Danon, A., S. Ben-Shimon, and Z. Ben-Zvi. 1986. Effect of exercise and heat exposure on percutaneous absorption of methyl salicylate. *Eur J Clin Pharmacol* 31:49-52.

das Gupta, V. 1980. High-pressure liquid chromatographic determination of salicylic acid in aspirin powder pharmaceutical dosage forms. *J Pharm Sci* 69(1):113-5.

Daston, G.P., B.F. Rehnberg B. Carver, E.H. Rogers, and R.J. Kavlock. 1988. Functional teratogens of the rat kidney. I. Colchicine, dinoseb, and methyl salicylate. *Fund Appl Toxicol* 11(3):381-400.

Davies, M. and R. Marks. 1976. Studies on the effect of salicylic acid on normal skin. *Br J Dermatol* 95:187-92.

Davies, M.G., D.Vella Briffa, and M.W. Greaves 1979. Systemic toxicity from topically applied salicylic acid. *Br Med J* 1: 661.

Davis, D.A.P., G.P. Daston, M.R. Odio, R.G. York, and A.L. Kraus. 1996. Maternal reproductive effects of oral salicylic acid in Sprague-Dawley rats. *Toxicol Lett* 84:135-41.

Davis, D.A.P., A.L. Kraus, G.A Thompson, M. Olerich, and M.R. Odio. 1997. Percutaneous absorption of salicylic acid after repeated (14-day) *in vivo* administration to normal, acnegenic or aged human skin. *J Pharm Sci* 86(8):896-9.

Davison, C., E.F. Zimmerman, and P.K. Smith. 1961. On the metabolism and toxicity of methyl salicylate. *J Pharmacol Exp Ther* 132:207-11.

Dawkins, P.D., J.N. McArthur, and M.J.H. Smith. 1970. The effect of sodium salicylate on the binding of long chain fatty acids to plasma proteins. *J Pharm Pharmacol* 22:405-10.

Dean, M., S. Penglis, and B. Stock. 1989. The pharmacokinetics of salicylate in the pregnant Wistar rat. *Drug Metab Dispos* 17(1):87-90.

Demerec, M., G. Bertani, and J. Flint. 1951. A survey of chemicals for mutagenic action on *E. coli*. *Am Natur* 85:119-36.

Doeglas, H.M. 1975. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 93(2):135-44.

Dong, Z., C. Huang, R.E. Brown, and W.-Y. Ma. 1997 Inhibition of activator protein 1 activity and neoplastic transformation by aspirin. *J Biol Chem* 272(15):9962-70.

Douek, E.E., H.C. Dodson, and L.H. Bannister 1983. The effects of sodium salicylate on the cochlea of guinea pigs. *J Layrngol Otol* 93:793-9.

Durnas C and Cusack. 1992. Salicylate intoxication in the elderly. Recognition and recommendations on how to prevent it. *Drugs Aging* 2(1):20-34.

Dwyer, C.M., R.H. McCloskey, and R.E.I. Kerr. 1994. Poisoning from topical salicylic acid. *Postgrad Med J* 70(820):146.

Ebron-McCoy, M.T., P.E. Beyer, L.A. Oglesby, and R.J. Kavlock. 1988. *In vitro* culture of postimplantation hamster embryos. *Reprod Toxicol* 2(1):31-6.

Ekwall, B. and D. Acosta. 1982. *In vitro* comparative toxicity of selected drugs and chemicals in HeLa cells, Chang liver cells, and rat hepatocytes. *Drug Chem Toxicol* 5(3):219-31.

Elder, D.J.E., A. Hague, D.J. Hicks, and C. Paraskeva. 1996. Differential growth inhibition by the aspirin metabolite salicylate in human colorectal tumor cell lines: Enhanced apoptosis in carcinoma and *in vitro*-transformed adenoma relative to adenoma cell lines. *Cancer Res* 56(10):2273-6.

Elias, P.M., E.R. Cooper, A. Korc, and B.E. Brown. 1981. Percutaneous transport in relation to stratum corneum structure and lipid composition. *J Invest Dermatol* 76(4):297-301.

Emudianughe, T.S. 1988. Possible genetic influence on conjugate formation in salicylic acid metabolism. *Arch int Pharmacodyn* 292:7-12.

Emudianughe, T.S., S.O. Oduleye, E.E. Ebadan, and S.D. Eneji. 1986. Sex differences in salicylic acid metabolism in Nigerian subjects. *Xenobiotica* 16(2):177-9.

Environmental Health Research and Testing, Inc. (1984) Methyl Salicylate: Reproduction and fertility assessment in CD-1 mice when administered by gavage. Final report (Nov). NTIS Report No. PB85-164283.

Erdoğan, D, S. Kadioğlu, and T. Peker. 1996. Demonstration of congenital anomalies in the joints of the forelimbs and hindlimbs caused by several pharmacological agents. *Anat Histol Embryol* 25(4):263-7.

Eriksson, M. 1969. Salicylate-induced foetal hemorrhage in two mouse strains. *Acta Pathol Microbiol Scand* 76:164-70.

Eriksson, M. 1970. Salicylate-induced fetal damage during late pregnancy in mice. *Acta Paediatr Scand* 59:517-22.

Eriksson, M. 1971. Salicylate-induced foetal damage during late pregnancy in mice: A comparison between sodium salicylate, acetylsalicyclic acid and salicylsalicylic acid. *Acta Pharmacol Toxicol* 29:250-6.

Eriksson, M. and K.S. Larsson. 1968. Premature birth induced in mice by salicylate. *Nature (London)*: 220:385.

Eriksson, M. and K.S. Larsson. 1971. Salicylate-induced foetal damage in two mouse strains: Studies on the distribution of ^{14}C-labelled salicylic acid. *Acta Pharmacol Toxicol (Copenh)* 29(23):256-64.

European Economic Community (EEC). 1998. EEC Cosmetics Directive 76/768/EEC, as amended through September 15, Annexes VI, Reference 3. Brussels:EEC.

Fabro, S., J.A. McLachlan, and N.M. Dames. 1984. Chemical exposure of embryos during the preimplantation stages of pregnancy: Mortality rate and intrauterine development. *Am J Obstet Gynecol* 148:929-38.

Farid, N.A., G.S. Born, W.V. Kessler, S.M. Shaw, and W.E. Lange. 1975. Improved colorimetric determination of salicylic acid and its metabolites in urine. *Clin Chem* 21(8):1167-8.

Farivar, R.S. and P. Brecher. 1996. Salicylate is a transcriptional inhibitor of the inducible nitric oxide synthase in cultured cardiac fibroblasts. *J Biol Chem* 271(49):31585-92.

Farivar, R.S., A.V. Chobanian, and P. Brecher. 1996 Salicylate or aspirin inhibits the induction of the inducible nitric oxide synthase in rat cardiac fibroblasts. *Circ Res* 78(5):759-68.

Feldmann, R.J. and H.I. Maibach. 1970. Absorption of some organic components through the skin in man. *J Invest Dermatol* 54(5):399-404.

Fisher, A.A. 1986. Compound ("synergistic") allergy to contactants. *Cutis* 38(2):101-2.

Flesch, P., A. Satanove, and C.S. Brown. 1955. Laboratory methods for studying percutaneous absorption and the chemical effects of topical agents upon human skin. *J Invest Dermatol* 25:289-300.

Flint, O.P., T.C. Ortin, and R.A. Ferguson. 1984. Differentiation of rat embryo cells in culture: Response following acute maternal exposure to teratogens and non-teratogens. *J Appl Toxicol* 4(2):109-16.

Foltinová, P. and J. Grones. 1997. *Euglena gracilis* as an eukaryotic test organism for detecting mutagens and antimutagens. *Mutat Res* 393(1-2): 1-6.

Food and Drug Administration (FDA). 1966. Chronic oral toxicity study of Methyl Salicylate using dogs and reproductive and developmental effects oral study of Methyl Salicylate using rats. Studies dated May. (Submitted by FDA in response to an FOI request - 1998; 33 pp.)[1]

FDA. 1984. Cosmetic product formulation and frequency of use data. FDA computer printout. Washington, DC:FDA.

FDA. 1998. Frequency of use of cosmetic ingredient. FDA computer printout. Washington, DC:FDA.

FDA. 1999. 21 CFR 352.10 - Sunscreen drug products for over-the-counter human use; subpart B - Sunscreen active ingredients. *Federal Register* 64 (98):27687.

Francis, B.M., Y.-S. Huang, P.C. Hartig, et al. 1990. Effects of murine cytomegalovirus on development: Lack of interactions of virus and sodium salicylate. *J Appl Toxicol* 10(1):43-6.

Fritz, H. and K. Giese. 1990. Evaluation of the teratogenic potential of chemicals in the rat. *Pharmacology* 40 (Suppl 1):1-28.

Fritz, H. and H.P. Suter. 1985. Postnatal development of young rats following the treatment of the dams with sodium salicylate during later periods of pregnancy. *Arzneim Forsch* 35(6):937-9.

Gabrielsson, J., L. Paalzow, S. Larsson, and I. Blomquist. 1985. Constant rate of infusion - Improvement of tests for teratogenicity and embryotoxicity. *Life Sci* 37(24):2275-82.

Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. *Brit J Industr Med* 27:1-18.

Gange, R.W., A. Soparkar, E. Matzinger, et al. 1986. Efficacy of a sunscreen containing butyl methoxydibenzoylmethane against ultraviolet A radiation in photosensitized subjects. *J Am Acad Dermatol* 15(3):494-9.

Gautman, S.C., K.R. Pindolia, C.J. Noth, et al. 1995. Chemokine gene expression in bone marrow stromal cells: Downregulation with sodium salicylate. *Blood* 86(7):2541-50.

Geber, W.F. 1977. Effects of central nervous system active and nonactive drugs on the fetal central nervous system. *Neurotoxicology* (Raven Press)1:585-93.

Geber, W.F., S.S. Lefkowitz, and C.Y. Hung. 1975. Effect of ascorbic acid, sodium salicylate, and caffeine on the serum interferon level in response to viral infection. *Pharmacology* 13(3):228-33.

Geber, W.F., S.S. Lefkowitz, and C.Y. Hung. 1975. Effect of morphine, hydromorphone, methadone, mescaline, trypan blue, vitamin A, sodium salicylate, and caffeine on the serum interferon level in response to viral infection. *Arch Int Pharmacodyn* 214(2):322-7.

Gennaro, A.R. 1990. *Remington's Pharmaceutical Sciences*, 18th edn. Easton, PA:Mack Publishing Co, 773, 768, 1112, 1114.

Gerberick, G.F., R.V. House, R. Fletcher, and C.A. Ryan. 1992. Examination of the local lymph node assay for use in contact sensitization risk assessment. *Fund Appl Toxicol* 19:428-45.

Germann, R., I. Schindera, M. Kuch, et al. 1996. Life-threatening salicylate poisoning following percutaneous absorption in a patient with ichthyosis vulgaris. *Hautarzt* 47(8):624-7.

Gip, L, and A. Hamfelt. 1976. Percutaneous absorption of betamethasone-17, 21-dipropionate, and salicylic acid during the treatment of psoriasis and eczema. *J Int Med Res* 4(2):106-10.

Giri, A.K., N. Adhikari, and K.A. Khan. 1996. Comparative genotoxicity of six salicylic acid derivatives in bone marrow cells of mice. *Mutat Res* 370:1-9.

Giroux, J., R. Granger, and P. Monnier. 1954. Comparative toxicity of methyl diethylacetylsalicylate and methyl salicylate. *Société Pharmacie Monpellier* (volume unknown):383-90

Glombitza, B.W. and P.C. Schmidt. 1994. Comparison of three new spectrophotometric methods for simultaneous determination of aspirin and salicylic acid in tablets without separation of pharmaceutical excipients. *J Pharm Sci* 83(5) 751-7.

Gloor, M. and B. Beier. 1984. Studies on the keratoplastic effect of salicylic acid, sulfur and a tenside mixture. *Z Hautkr* 59(24):1657-60.

Goh, C.L. and S.K. Ng. 1986. Contact allergy to salicylic acid. *Contact Derm* 14(2):114.

Goldenthal EI. 1971. A compilation of LD50 values in newborn and adult animals. *Toxicol Appl Pharmacol* 18:185-207

Goldman, A.S. and W.C. Yakovac. 1963. The enhancement of salicylate teratogenicity by maternal immobilization in the rat. *J Pharmacol Exp Ther* 142:351-7.

Goldsmith, L.A. 1979. Salicylic acid. *Int J Dermatol* 18(1):32-6.

Grant, J., ed. 1972. *Hackh's Chemical Dictionary*, 4th edn. New York, NY:McGraw-Hill Book Co., 125, 402, 426, 541, 594, 621.

Greenaway J.C., D.H. Bark, and M.R. Juchau. 1984. Embryotoxic effects of salicylates: Role of biotransformation. *Toxicol Appl Pharmacol* 74:141-9.

Greenaway, J.C., T.H. Shepard, A.G. Fantel, and M.R. Juchau. 1982. Sodium salicylate teratogenicity *in vitro*. *Teratology* 26(2):167-71.

Guillaume, J.C., J. DeRigal, J.L. Levèque, et al. 1981. Study of the correlation between transepidermal water loss and percutaneous penetration of steroids. *Dermatologica* 162:380-90.

Gulamhusein, A.P., C. Harrison-Sage, F. Beck, and A. Al-Alousi. 1980. Salicylate-induced teratogenesis in the ferret. *Life Sci* 27:1799-1805.

Haarmann and Reimer. 1991. Survey of safety studies (acute dermal toxicity, acute oral toxicity, skin irritation, ocular irritation, sensitization, and *in vitro* and *in vivo* mutagenicity) on Neo Heliopan, Type OS (Octyl Salicylate). Fr 91/136. Unpublished data submitted by CTFA. 10 pp.[1]

Haarmann and Reimer. 1992. Chemical properties and safety information on 2-ethylhexyl salicylate (Octyl Salicylate). Unpublished data submitted by CTFA. 3 pp.[1]

Hackman, R.M. and L.S. Hurley. 1984. Interactions of salicylate, dietary zinc, and genetic strain in teratogenesis in rats. *Teratology* 30(2):225-36.

Harada, K., T. Murakami, E. Kawasaki, et al. 1993. *In-vitro* permeability to salicylic acid of human, rodent, and shed snake skin. *J Pharm Pharmacol* 45(5):414-8.

Harrison Research Laboratories, Inc.(HRL). 1993a. Cumulative irritation test of a gel containing 2% Salicylic Acid. HRL Panel #93-356. Ref #18254.05. Project #7536. Final report dated Sept 20. Unpublished data submitted by CTFA. 8 pp.[1]

HRL 1993b. Repeated insult patch test of a gel containing 2% Salicylic Acid. HRL Panel #93-125 (1). Ref #18254.03. Project #7536. Final report dated Sept 10. Unpublished data submitted by CTFA. 17 pp.[1]

HRL 1993c. Phototoxicity test of a gel containing 2% Salicylic Acid. HRL Panel #93-511T (1). Ref #18254.06. Project #7536. Final report dated July 26. Unpublished data submitted by CTFA. 8 pp.[1]

HRL. 1993d. Photoallergy test of a gel containing 2% Salicylic Acid. HRL Panel #93-511A (1). Ref #18254.07. Project #7536. Final report dated Aug 22. Unpublished data submitted by CTFA. 17 pp.[1]

HRL. 1997a. Repeated insult patch test of a gel containing 2% Salicylic Acid. HRL Panel #97-103 (1). Ref #21544.03. Project #7696. Final report dated Mar 24. Unpublished data submitted by CTFA. 17 pp.[1]

HRL. 1997b. Phototoxicity test of a gel containing 2% Salicylic Acid. HRL Panel #97-502T (1). Ref #21544.06. Project #7696. Final report dated Feb 14. Unpublished data submitted by CTFA. 9 pp.[1]

HRL. 1997c. Photoallergy test of a gel containing 2% Salicylic Acid. HRL Panel #97-502A (1). Ref #21544.07. Project #7696. Final report dated Mar 28. Unpublished data submitted by CTFA. 18 pp.[1]

Hart, E.R. 1947. The toxicity and analgetic potency of salicylamide and certain of its derivatives as compared with established analgetic-antipyretic drugs. *J Pharmacol Exp Ther* 89:205-9.

Hasegawa, R., Y. Nakaji, Y. Kurokawa, and M. Tobe. 1989. Acute toxicity tests on 113 environmental chemicals. *Sci Rep Res Inst Tohoku Univ, -C* 36(1-4):10-16.

Heng, M.C.Y. (1987) Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. *Cutis* 39(5):442-4.

Hial, V., M.C.F. De Mello, Z. Horakova, and M.A. Beaven. 1977. Antiproliferative activity of anti-inflammatory drugs in two mammalian cell culture lines. *J Pharmacol Exp Ther* 202(2):446-54.

Higo, N., S. Sato, T. Irie, and K. Uekama. 1995. Percutaneous penetration and metabolism of salicylic acid derivatives across hairless mouse skin in diffusion cell *in vitro*. *STP Pharma Sci* 5(4):302-8.

Hill, J.B. 1971. Experimental salicylate poisoning: Observations on the effects of altering blood pH on tissue and plasma salicylate concentrations. *Pediatrics* 47(4):658-65.

Hindson, C. 1977. Contact eczema from methyl salicylate reproduced by oral aspirin (acetyl salicylic acid). *Contact Derm* 3:348-9.

Howrie, D.L., R. Moriarty, and R. Breit. 1985. Candy flavoring as a source of salicylate poisoning *Pediatrics* 75(5):869-71.

Huang, C., W.-Y. Ma, D. Hanenberger, et al. 1997 Inhibition of ultraviolet B-induced activator protein-1 (AP-1) activity by aspirin in AP-1-luciferase transgenic mice. *J Biol Chem* 272(42): 26325-31.

Huber, C., and E. Christophers. 1977. 'Keratolytic' effect of salicylic acid. *Arch Derm Res* 257:293-7.

Huntingdon Life Sciences. (1998a) Physicochemical properties of Hallbrite BHB (Butyloctyl Salicylate). CCM 001/983015. Report dated Oct 29. Unpublished data submitted by CTFA. 2 pp.[1]

Huntingdon Life Sciences. (1998b) Hallbrite BHB (Butyloctyl Salicylate): Acute dermal toxicity study in rats. Study no. 98-1766 dated Aug 19. Unpublished data submitted by CTFA. 2 pp.[1]

Huntingdon Life Sciences. (1998c) Hallbrite BHB (Butyloctyl Salicylate): A 4-week oral toxicity study in the rat. Study no. 98-2570 dated Oct 12. Unpublished data submitted by CTFA. 2 pp.[1]

Huntingdon Life Sciences. (1998d) Hallbrite BHB (Butyloctyl Salicylate): Guinea pig maximization test. (Method of Magnusson and Kligman.) Study no. 98-1767 dated Aug 19. Unpublished data submitted by CTFA. 3 pp.[1]

Huntingdon Life Sciences. (1998e) Hallbrite BHB (Butyloctyl Salicylate):Bacterial mutation assay. CCM 006/982735. Dated Sept 30. Unpublished data submitted by CTFA. 2 pp.[1]

Huntingdon Life Sciences. (1998f) Hallbrite BHB (Butyloctyl Salicylate):*In vitro* mammalian chromosome aberration test in human lymphocytes. Study no. CCM/007. Report no. CCM007/983236 dated Sept 30. Unpublished data submitted by CTFA. 3 pp.[1]

Infurna, R, B. Beyer, L. Twitty, G. Koehler, and W. Daughtrey. 1990. Evaluation of the dermal absorption and teratogenic potential of methyl salicylate in a petroleum based grease. Abstract P47. *Teratology* 41(5):566.

Ishidate, M., Jr., T. Sofuni, K. Yoshikawa K, et al. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Fd Chem Toxicol* 22:623-36.

Ishii, T., J.M. Bernstein, and K. Balogh, Jr. 1967. Distribution of tritium-labeled salicylate in the cochlea. *Ann Otol Rhinol Laryngol* 76:368-76.

Ivy Laboratories. 1993a. Final report on human phototoxicity bioassay of a 2% Salicylic Acid cream dated Aug 9. Sponsor study DRD #BCS0070(S). KGL Protocol #3112. Unpublished data submitted by the Procter & Gamble Co. 20 pp.[1]

Ivy Laboratories. 1993b. Final report on the determination of the photocontact allergenic potential of two topically applied test materials (one of which is a 2% Salicylic Acid cream) by means of the photocontact allergenicity test dated Sept 14. Sponsor study DRD #BCS0080. KGL Protocol #3111. Unpublished data submitted by the Procter & Gamble Co. 20 pp.[1]

Ivy Laboratories. 1993c. Final report on the determination of the photocontact allergenic potential of a topically applied test material (a 2% Salicylic Acid cream) by means of the photocontact allergenicity test dated Sept 29. Sponsor study DRD #BCS0070S. KGL Protocol #3113. Unpublished data submitted by the Procter & Gamble Co. 20 pp.[1]

Jackson, A.V. 1948. Toxic effects of salicylate on the fœtus and mother. *J Pathol Bacteriol* 60:587-93.

Janssen, K., P.C.H. Hollman, E. Reichman, et al. 1996. Urinary salicylate excretion in subjects eating a variety of diets shows that amounts of bioavailable salicylates in foods are low. *Am J Clin Nutr* 64(5):743-7.

Jenner, P.M., E.C. Hagan, J.M. Taylor, E.L. Cook, and O.G. Fitzhugh. 1964. Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet Toxicol* 2:237-43.

Johansson, J and A. Lahti 1988. Topical non-steroidal anti-inflammatory drugs inhibit non-immunological immediate contact reactions. *Contact Derm* 19(3): 161-5.

Joschko, M.A., I.E. Dreosti, and R.S. Tulsi. 1993. The teratogenic effects of salicylic acid on the developing nervous system in rats *in vitro*. *Teratology* 48(2):105-14.

Jung, T.T., C.-K. Rhee, C.S. Lee, Y.-S. Park, and D.-C. Choi. 1993. Ototoxicity of salicylate, nonsteroidal anti-inflammatory drugs, and quinine. *Otolaryngol Clin North Am* 26(5):791-810.

Kabara, J.J., ed. 1984. *Cosmetic and Drug Preservation Principles and Practice*. New York, NY:Marcel Dekker, Inc., 616, 672-3

Kaviock R.J., N. Chernoff, and E.H Rogers. 1985 The effect of acute maternal toxicity on fetal development in the mouse *Teratog Carcinog Mutagen* 5(1):3-13

Kaviock, R.J., N. Chernoff, E. Rogers, et al. 1982 An analysis of fetotoxicity using biochemical endpoints of organ differentiation. *Teratology* 26(2):185-94

Kawachi, T., T. Komatsu, T. Kada, et al. 1980a. Results of recent studies on the relevance of various short-term screening tests in Japan. In: *The Predictive Value of Short-Term Screening Tests in Carcinogenicity Evaluation. Appl Methods Oncol* 3:253-67.

Kawachi, T., T. Yahagi, T. Kada, et al. 1980b. Cooperative programme on short-term assays for carcinogenicity in Japan. *IARC Sci Publ* 27:323-30.

Keplinger, M.L., P.L. Wright, J.B. Plank, and J.C. Calandra. 1974. Teratologic studies with FD&C Red No. 2 in rats and rabbits. *Toxicol Appl Pharmacol* 28:209-15.

Kershaw, R.A., D.C. May, J.R. Bianchine,and N. Gerber. 1987. Disposition of aspirin and its metabolites in the semen of man. *J Clin Pharmacol* 27(4):304-9.

Khera, K.S. 1991. Chemically induced alterations in maternal homeostasis and histology of conceptus: Their etiologic significance in rat fetal anomalies. *Teratology* 44(3):259-97.

Khera, K.S. and C. Whalen1988. Detection of neuroteratogens with an *in vitro* cytotoxicity assay using primary monolayers cultured from dissociated foetal rat brains. *Toxic in Vitro* 2(4):257-73.

Kimber, I., J. Hilton, P.A. Botham, et al. 1991. The murine local lymph node assay: Results of an inter-laboratory trial. *Toxicol Lett* 55(2):203-13.

Kimber, I., J. Hilton, R.J. Dearman, et al. 1995 An international evaluation of the murine local lymph node assay and comparison of modified procedures. *Toxicology* 103(1):63-73.

Kimmel, C.A., J.G. Wilson, and H.J. Schumacher. 1971. Studies on metabolism and identification of the causative agent in aspirin teratogenesis in rats. *Teratology* 4:15-24.

Kin, A.N. and T. Nakatsui. 1998. Salicylic acid revisited. *Intl J Dermatol* 37:335-42.

Kirchhoefer, R.D. 1980. Simultaneous determination of aspirin and salicylic acid in bulk aspirin and in plain, buffered, and enteric-coated tablets by high-pressure liquid chromatography with UV and fluorescence detectors. *J Pharm Sci* 69(10):1188-91

Klein-Schwartz, W. 1983 Salicylate poisoning. *Ear Nose Throat J* 62(2):69-74.

Kleinerman, E.S., J.S. Louie, L.M. Wahl, and A.V. Muchmore. 1981. Pharmacology of human spontaneous monocyte-mediated cytotoxicity. I. Enhancement by salicylates and steroids. *Arthritis Rheum* 24(6):774-80.

Kligman, A.M. 1966. The identification of contact allergans by human assay. III. The maximization test: A procedure for screening and rating contact sensitizers. *J Invest Dermatol* 47:393-409.

Kligman, L.H. and A.M. Kligman. 1979 The effect on rhino mouse skin of agents which influence keratinization and exfoliation. *J Invest Dermatol* 73(5):354-8.

Koren, G. 1993. Medications which can kill a toddler with one tablet or teaspoonful. *J Toxicol Clin Toxicol* 31(3):407-13.

Kornreich, C., Z.S. Zheng, G.Z. Xue, and J.H. Prystowsky. 1996. A simple method to predict whether topical agents will interfere with phototherapy. *Cutis* 57(2):113-8.

Koshakji, R.P. and A.R. Schulert. 1973. Biochemical mechanisms of salicylate teratology in the rat. *Biochem Pharmacol* 22:407-16.

Kristensen, B. and O. Kristensen. 1991. Topical salicylic acid interferes with UBV therapy for psoriasis. *Acta Derm Venereol* 71(1):37-40.

Krivosíková, Z., V. Spustová, and R. Dzúrik. 1996. A highly sensitive HPLC method for simultaneous determination of acetylsalicylic, salicylic and salicyluric acids in biologic fluids: Pharmacokinetic, metabolic and monitoring implications. *Methods Find Exp Clin Pharmacol* 18(8):527-32.

Kubinski, H., G.E. Gutzke, and Z.O. Kubinski. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. *Mutat Res* 89:95-136.

Kuboyama, N. and A. Fujii. 1992. Mutagenicity of analgesics, their derivatives, and anti-inflammatory drugs with S-9 mix of several animal species. *J Nihon Univ Sch Dent* 34(3):183-95.

Kurosaki, Y., S.-I. Hisaichi, C. Hamada, T. Nakayama, and T. Kimura. 1988. Effects of surfactants on the absorption of salicylic acid from hamster cheek pouch as a model of keratinized oral mucosa. *Int J Pharm* 47:13-19.

Kurosaki, Y., T. Takatori, H. Nishimura, T. Nakayama, and T. Kimura. 1991. Regional variation in oral mucosal drug absorption: Permeability and degree of keratinization in hamster oral cavity. *Pharm Res* 8(10):1297-301.

Kyle, M.E. and J.J. Kocsis. 1985. The effect of age on salicylate-induced nephrotoxicity in male rats. *Toxicol Appl Pharmacol* 81(2):337-47.

Lachapelle, J.-M. and B. Leroy. 1990. Allergic contact dermatitis to colophony included in the formulation of flexible collodion BP, the vehicle of a salicylic and lactic acid wart paint. *Dermatol Clin* 8(1):143-6.

Lacroix, R. and J. Ferragne. 1964. Methyl salicylate poisoning. I. Toxic effects in conscious and in anesthesized dogs. *Société de Pharmacie de Lyon* (Vol unknown):129-38.

Lahti, A. (1980) Non-immunologic contact urticaria. *Acta Dermato-Venereol Suppl* 60(91):1-49.

Lamb, J., Gulati, D., Choudhury, H., Chambers, R., Sabharwal, P. 1997a. Reproductive toxicology. Methyl salicylate. *Environ Health Perspect* 105 (Suppl 1):321-2.

Lamb, R., Reel, J.R., Tyl, R., Lawton, A.D. 1997b. Reproductive toxicology. Methyl salicylate. *Environ Health Perspect* 105(Suppl 1):323-4.

Lansdown, A.B.G. 1970. Histological changes in the skeletal elements of developing rat fetuses following treatment with sodium salicylate. *Fd Cosmet Toxicol* 8:647-53.

Larsson, K.S. and H. Boström. 1965. Teratogenic action of salicylates related to the inhibition of mucopolysaccharide synthesis. *Acta Paediatr Scand* 54:43-8.

Larsson, K.S., H. Boström, and B.-Ericson. 1963. Salicylate-induced malformation in mouse embryos. *Acta Pædiatr* 52(1):36-40.

Larsson, K.S. and M. Erikkson. 1966. Salicylate-induced fetal death and malformations in two mouse strains. *Acta Paediatr Scand* 55:569-76.

LaWall & Harrisson Research Laboratories, Inc. 1964. Study of Methyl Salicylate on rats. L&H 58188. (Submitted by FDA in response to an FOI request - 1998; 120 pp.)[1]

Leberco•Celsis Testing. 1996a. Acute oral toxicity study (FHSA) on Butyloctyl Salicylate. Laboratory Project ID 967630 dated April 9. Unpublished data submitted by CTFA. 2 pp.[1]

Leberco•Celsis Testing. 1996b. Primary dermal irritation in rabbits (FHSA) of Butyloctyl Salicylate. Laboratory Project ID 967629 dated April 19. Unpublished data submitted by CTFA. 2 pp.[1]

Leberco•Celsis Testing. 1996c. Primary eye irritation (FHSA) of Butyloctyl Salicylate. Laboratory Project ID 967628 dated April 11. Unpublished data submitted by CTFA. 2 pp.[1]

Lee, T.Y. and T.H. Lam. 1990. Patch testing of 11 common herbal topical medicaments in Hong Kong. *Contact Derm* 22:137-40.

Lester, H. and K. Davis. 1984. Letter to the editor - Oil of wintergreen. *Vet Hum Toxicol* 26(4):308.

Lewis, R.J., Sr. 1993a. *Hazardous Chemicals Desk Reference*, 3rd edn. New York, NY:Van Nostrand Reinhold, 877, 1124, 1172.

Lewis, R.J., Sr. 1993b. *Hawleys's Condensed Chemical Dictionary*, 12th edn. New York: Van Nostrand Reinhold Co, 722, 780, 1019, 1068.

Lide, D.R., ed. 1993. *CRC Handbook of Chemistry and Physics*, 74th edn. Boca Raton, FL:CRC Press, Inc, 3-455-7.

Liebelt, E.L. and M.W. Shannon. 1993. Small doses, big problems: A selected review of highly toxic common medications. *Pediatr Emerg Care* 9(5):292-7.

Lindsey, C.P. 1968. Two cases of fatal salicylate poisoning after topical application of antifungal solution. *Med J Aust* 1:353-4.

Litovitz, T. and A. Manoguerra. 1992. Comparison of pediatric poisoning hazards: An analysis of 3.8 million exposure incidents: A report from the American Association of Poison Control Centers. *Pediatrics* 89(6 Part 1):999-1006.

Lodén, M., P. Boström, and M. Kneczke 1995. Distribution and keratolytic effect of salicylic acid and urea in human skin. *Skin Pharmacol* 8(4):173-8.

Loveday, D.E. 1961. An *in vitro* method for studying percutaneous absorption. *J Soc Cosmet Chem* 12:224-39.

Lowe, N.J., S.H. Dromgoole, J. Sefton, T. Bourget, and D. Weingarten. 1987. Indoor and outdoor efficacy testing of a broad-spectrum sunscreen against ultraviolet A radiation in psoralen-sensitized subjects. *J Am Acad Dermatol* 17(2):224-30.

Luderschmidt, C. and G. Plewig. 1975. Die chronische perkutane Salizylsäureintoxikation. *Hautarzt* 26:643-6.

Lukas, J.C., T.S. Rosenkrantz, J.R. Raye, P.J. Porte, and A.F. Philipps. 1987. Intrauterine growth retardation after long-term maternal salicylate administration in the rabbit. *Am J Obstet Gynecol* 156:245-9.

Marcus, F., J.L. Colaizzi, and H. Barry, III. 1970. pH effects on salicylate absorption from hydrophilic ointment. *J Pharm Sci* 59:1616-20.

Markland, W.R. 1976. Sunscreens: Safe and effective cosmetic-drugs. *Cosmet Toilet* 91:79-81.

Marks, R., M. Davies, and A. Cattell. 1975. An explanation for the keratolytic effect of salicylic acid. *J Invest Dermatol* 64:283.

Marsk, L. 1980. Teratology study in the mouse using a prostaglandin and a prostaglandin synthetase inhibitor. *Toxicol Lett* 6(6):423-6.

Maruta, H., K. Minami, T. Yamagata, and K. Noda. 1977. Percutaneous absorption of methyl salicylate from medicated plaster in mice and humans. *Kurume Med J* 23(3):131-7.

Mason, W.D. 1980. Comparative plasma salicylate and urine salicylurate levels following administration of aspirin, magnesium salicylate, and choline magnesium trisalicylate. *J Pharm Sci* 69(11):1355-6.

McCann, J., E. Choi, E. Tamasaki, and B.N. Ames. 1975. Detection of carcinogens as mutagens in the *Salmonella*/microsome test: Assay of 300 chemicals. *Proc Natl Acad Sci USA* 72:5135-9.

McGarrity, C., N. Samani, F. Beck, and A. Gulamhusein. 1981. The effect of sodium salicylate on the rat embryo in culture: An *in vitro* model for the morphological assessment of teratogenicity. *J Anat* 133(Pt 2):257-69.

McMahon, T.F., J.J. Diliberto, and L.S. Birnbaum. 1990. Effects of age and dose on disposition and metabolism of salicylic acid in male Fischer 344 rats. *Drug Metab Dispos* 18(4):494-503.

McMahon, T.F., S.A. Stefanski, R.E. Wilson, et al. 1991. Comparative acute nephrotoxicity of salicylic acid, 2,3-dihydroxybenzoic acid, and 2,5-dihydroxybenzoic acid in young and middle aged Fischer 344 rats. *Toxicology* 66(3):297-311.

Megwa, S.A., H.A.E. Benson, and M.S. Roberts. 1995. Percutaneous absorption of salicylates from some commercially available topical products containing methyl salicylate or salicylate salts in rats. *J Pharm Pharmacol* 47(11):891-6.

Miaskiewicz, S.L., C.A. Shively, and E.S. Vesell. 1982. Sex differences in absorption kinetics of sodium salicylate. *Clin Pharmacol Ther* 31(1):30-7.

Mitchell, C., R. Brummett, D. Himes, and J. Vernon. 1973. Electrophysiological study of the effect of sodium salicylate upon the cochlea. *Arch Otolaryngol* 98:297-301.

Miyachi, Y. and M. Takigawa. 1983. Mechanisms of contact photosensitivity in mice. III. Predictive testing of chemicals with photoallergenic potential in mice. *Arch Dermatol* 119(9):736-9.

Moore, T.J., M.J. Joseph, B.W. Allen, and L.A. Coury Jr. 1995. Enzymatically amplified voltammetric sensor for microliter sample volumes of salicylate. *Anal Chem* 67(11):1896-1902.

Moore-Robinson, M. and R.P. Warin. 1967. Effect of salicylates in urticaria. *Br Med J* 4:262-4.

Morra, P., W.R. Bartle, S.E. Walker SE, et al. 1996. Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother* 30(9):935-40.

Morrissey, R.E., J.C. Lamb IV, R.W. Morris, et al. 1989. Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. *Fund Appl Toxicol* 13:747-7.

Mortelmans, K., S. Haworth, T. Lawlor, et al. 1986. *Salmonella* mutagenicity tests. II. Results from the testing of 270 chemicals. *Environ Mutagen* 8 (Suppl 7):1-119.

Mummery, C.L., C.E. van den Brink, P.T. van der Saag, and S.W. de Laat. 1984. A short-term screening test for teratogens using differentiating neuroblastoma cells *in vitro*. *Teratology* 29:271-9.

Murugesh N., V.R. Kumar, S. Vembar, and C. Damodaran. 1981. Studies on erythrocyte membrane. V. Haemolytic effect of methylsalicylate and its possible mechanisms. *Toxicol Lett* 9(3):225-9.

National Academy of Sciences (NAS). 1996. *Food Chemicals Codex*, 4th edn. Washington, D.C.:National Academy Press, 534.

Neubert, R, D. Partyka, W. Wohlrab, et al. 1990. Penetration of salicylic acid and salicylate into the multilayer membrane system and into the human horny layer. *Dermatol Mon.schr* 176(11):711-6.

Nezádalová, E., J. Elis, and H. Rašková. 1973. Sodium salicylate toxicity and pregnancy in mice. *J Pharm Pharmacol* 25(1):80-1.

Nikitakis, J.M. and G.N. McEwen Jr, eds. 1990a. *CTFA Compendium of Cosmetic Ingredient Composition - Specifications*. Washington, D.C.:CTFA.

Nikitakis, J.M. and G.N. McEwen Jr, eds. 1990b. *CTFA Compendium of Cosmetic Ingredient Composition - Descriptions II*. Washington, D.C.:CTFA.

Nishihata, T., C. Ikawa, Y. Saitoh, and K. Sakai. 1988. Glycogenolysis in the rat isoalted perfused liver as a measure of chemically induced liver toxicity. *J Pharm Pharmacol* 40(5):333-6.

Noble, E., L. Janssen, and P.J. Dierckx. 1997. Comparative cytotoxicity of 5-aminosalicylic acid (mesalazine) and related compounds in different cell lines. *Cell Biol Toxicol* 13(6):445-51.

Ojiambo, H.P. 1971a. Absorption, transport and biotransformation of methylsalicylate in the dog. *East Afr Med J* 48(7):318-21.

Ojiambo, H.P. 1971b. Hindlimb metabolism in dogs intoxicated with methylsalicylate. *East Afr Med J* 48(9):476-81.

Ojiambo, H.P. 1971c. Certain aspects of metabolism in myopathies induced by methylsalicylate intoxication in the dog. *East Afr Med J* 48(6):243-6.

Ojiambo, H.P. 1972. Myocardial mechanics, metabolism and energetics in hyperkalaemic cardiomyopathy in the dog. *Afr J Med Sci* 3:247-56.

Ojiambo, H.P. 1975. The cardiomyopathyl associated with methylsalicylate. *Postgrad Med J* 51:144-9.

Ojiambo, H.P., R. Petrie, J. Dusek, and G.A. Klassen. 1972. Acute hyperkalemic cardiomyopathy in the dog. *Recent Advan Stud Cardiac Struct Metab* 1:579-87.

Okumura, K., I.P. Lee, and R.L. Dixon. 1975. Permeability of selected drugs and chemicals across the blood-testis barrier of the rat. *J Pharmacol Exp Ther* 194(1):89-95.

Opdyke DL. 1978. Methyl Salicylate. *Fd Cosmet Toxicol* 16(Suppl 1):821-5.

Overman, D.O. and J.A. White. 1983. Comparative teratogenic effects of methyl salicylate applied orally or topically to hamsters. *Teratology* 28(3):421-6.

Packman, E.W., D.D. Abbott, B.M. Wagner, and J.W.E. Harrisson. 1961. Chronic oral toxicity of oil sweet birch (methyl salicylate). *Pharmacologist* 3:62.

Palermo, P.J. and J.B. Lundberg. 1979. Simulataneous programmed temperature gas chromatographic assay of zinc undecylenate, salicylic acid and dichlorophene in an aerosol foot powder. *Can J Pharm Sci* 14(1):21-3.

Panse, P., P. Zeiller, and K.H. Sensch. 1974. Percutaneous absorption of anti-inflammatory substances. *Arzneimittelforschung* 24(9):1298-301.

Pascher, F. 1978. Systemic reactions to topically applied drugs. *Int J Dermatol* 17(10):768-75.

Patriarca, G., A. Venuti, D. Schiavino, and G. Fais. 1976. Intolerance to aspirin: Clinical and immunological studies. *Z Immun-Forsch* 151(4):295-304.

Patrick, E., A. Burkhalter, and H.I. Maibach. 1987. Recent investigations of mechanisms of chemically induced skin irritation in laboratory mice. *J invest Dermatol* 88(3 Suppl):24s-31s.

Patrick, E., H.I. Maibach, and A. Burkhalter. 1985. Mechanisms of chemically induced skin irritation. I. Studies of time course, dose response, and components of inflammation in the laboratory mouse. *Toxicol Appl Pharmacol* 81(3):476-90.

Peskar, B.M., U. Hoppe, K. Lange, and B.A. Peskar. 1988. Effects on non-steroidal anti-inflammatory drugs on rat gastric mucosal leukotriene C_4 and prostanoid release: Relation to ethanol-induced injury. *Br J Pharmacol* 93(4):937-43.

Piérard G.E., N. Nikkels-Tassoudji J.E. Arrese, C. Piérard-Franchimont, and J.L. Lévêque. 1997. Dermo-epidermal stimulation elicited by a β-lipo-hydroxyacid: A comparison with salicylic acid and all-trans-retinoic acid. *Dermatology* 194(4):398-401.

Pierce, J.W., M.A. Read, H. Ding, F.W. Luscinskas, and T. Collins. 1996. Salicylates inhibit IκB-α phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration. *J Immunol* 156(10):3961-9.

Polano, M.K. and M. Ponec. 1976. Dependence of corticosteroid penetration on the vehicle. *Arch Dermatol* 112(5):675-80.

Porat-Soldin, O. and S.J. Soldin. 1992. Preliminary studies on the *in vitro* and *in vivo* effect of salicylate on sperm motility. *Ther Drug Monit* 14(5):366-70.

Pratzel, H.G., E. Schubert, and N. Muhanna. 1990. Pharmacokinetic study of percutaneous absorption of salicylic acid from baths with salicylate methyl ester and salicylic acid. *Z Rheumatol* 49(4):185-91.

Procter and Gamble Company. 1999a. Human safety assessment for developmental/reproductive toxicity of Salicylic Acid in a typical facial cosmetic product. Unpublished data submitted by the Procter and Gamble Company. 16 pp.[1]

Procter and Gamble Company. 1999b. Skin irritation potential and pH of a Salicylic Acid-containing facial cosmetic product. Unpublished data submitted by the Procter and Gamble Company. 5 pp.[1]

Prokopovich, N,N. 1963, Experimental data on the pharmacology of salicylanilide, 4',5-dibromosalicyl-anilide and sodium caprylate. *Farmakol i Toksikol* 26(4):467-72.

Pryor, G.T., E.T. Uyeno, H.A. Tilson, and C.L. Mitchell. 1983. Assessment of chemicals using a battery of neurobehavioral tests: A comparative study. *Neurobehav Toxicol Teratol* 5:91-117.

Rabinowitz, J.L. and D. Baker. 1984. Absorption of labeled triethanolamine salicylate in human and canine knee joints. II. *J Clin Pharmacol* 24 (11-2):532-9.

Rabinowitz, J.L., E.S. Feldman, A. Weinberger, and H.R. Schumacher. 1982. Comparative tissue absorption of oral ^{14}C-aspirin and topical triethanolamine ^{14}C-salicylate in human and canine knee joints. *J Clin Pharmacol* 22(1): 42-8.

Raghoebar, M., W.B. Van den Berg, and C.A. Van Ginneken. 1988. Mechanisms of cell association of some non-steroidal anti-inflammatory drugs with isolated leucocytes. *Biochem Pharmacol* 37(7):1245-50.

Rapoport, S. and G.M. Guest. 1945. The effect of salicylates on the electrolyte structure of the blood plasma. I. Respiratory alkalosis in monkeys and dogs after sodium and methyl salicylate; the influence of hypnotic drugs and of sodium bicarbonate on salicylate poisoning. (Journal and volume unknown):759-68.

Raschke, R., P.A. Arnold-Capell, R. Richeson, and S.C. Curry. 1991. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 151(3):591-3.

Rempe, J.M. and L.G. Santucci. 1997. *CTFA List of Japanese Cosmetic Ingredients*, 3rd edn. Washington, D.C.:CTFA, 65, 70, 108, 117.

Research Triangle Institute. 1984. Methyl Salicylate: Reproduction and fertility assessment in CD-1 mice when administered by gavage. NTIS Report No. PB84-241140.

Robert, A. 1981. Gastric cytoprotection by sodium salicylate. *Prostaglandins* 21(Suppl):139-46.

Roberts, D.L., R. Marshall, and R. Marks. 1980. Detection of the action of salicylic acid on the normal stratum corneum. *Br J Dermatol* 103:191-6.

Roberts, M.S., W.A. Favretto, A. Meyer, M. Reckmann, and T. Wongseelashote. 1982. Topical bioavailability of methyl salicylate. *Aust N Z J Med* 12(3):303-5.

Roberts, M.S. and E. Horloch. 1978. Effect of repeated skin application on percutaneous absorption of salicylic acid. *J Pharm Sci* 67(12):1685-7.

Robinson, S.M., M. Poncet, J. Ferracin, J. Czernielewski, and M. Verschoore. 1994. Chronic topical application of all-trans-retinoic acid in man does not affect corneocyte surface area. *Skin Pharmacol* 7(4):176-80.

Rosenkranz, B., C. Fischer, C.O. Meese, and J.C. Frölich. 1986. Effects of salicylic and acetylsalicylic acid alone and in combination on platelet aggregation and prostanoid synthesis in man. *Br J Clin Pharmacol* 21:309-17.

Rudzki, E. and A. Koslowska. 1976. Sensitivity to salicylic acid. *Contact Derm* 2:178-82.

Rumyantsev, G.I., S.M. Novikov, V.E. Andrusov, N.N. Mel'nikova, and L.N. Semenovykh. 1992. Hygienic standardization of methyl salicylate in workplace air. *Gig Sanit* 57(7-8):28-31.

Ryder, H.W., M. Shaver, and E.B. Ferris, Jr. 1945. Salicylism accompanied by respiratory alkalosis and toxic encephalopathy. Report of a fatal case. *N Engl J Med* 232(21):617-21.

Sakitani, K., H. Kitade, K. Inoue, et al. 1997. The anti-inflammatory drug sodium salicylate inhibits nitric oxide formation induced by interleukin-1β at a translational step, but not at a transcriptional step, in hepatocytes. *Hepatology* 25(2):416-20.

Sado, I. (1973) Synergistic toxicity of official permissible preservative food additives. *Jpn J Hyg* 28(5):463-76.

Salako, Q, E.O. Fadiran, and W.O.A Thomas. 1989. Detection and determination of salicylic acid impurity in aspirin tablet formulations by high performance liquid chromatography. *Afr J Med Med Sci* 18(3):215-8.

San, R.H.C. and Chan, R.I.M. 1987. Inhibitory effect of phenolic compounds on aflatoxin B_1 metabolism and induced mutagenesis. *Mutat Res* 177:229-39.

Sax, N.I. 1979. *Dangerous Properties of Industrial Materials*, 5th edn. New York, NY:Van Nostrand Reinhold Co., 832, 962-3, 989.

Schuppli, R., R. Schneeberger, H. Seiler, et al. 1972 Toxicity of salicylic acid in dermatology. *Dermatologica* 144(4):248-52.

Schwenger, P., P. Bellosta, I. Vietor, et al. 1997 Sodium salicylate induces apoptosis via p38 mitogen-activated protein kinase but inhibits tumor necrosis factor-induced c-Jun N-terminal kinase/ stress-activated protein kinase activation. *Proc Natl Acad Sci USA* 94(7):2869-73.

Schwenger, P., E.Y. Skolnik, and J. Vilček. 1996. Inhibition of tumor necrosis factor-induced p42/p44 mitogen-activated protein kinase activation by sodium salicylate. *J Biol Chem* 271(14):8089-94.

Seidenberg, J.M., D.G. Anderson, and R.A. Becker. 1986. Validation of an *in vivo* developmental toxicity screen in the mouse. *Teratog Carcinog Mutagen* 6:361-74.

Seiler, J.P. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short-term test. *Mutat Res* 46:305-10.

Sharpe, G.L, K.S. Larsson, and B. Thalme. 1975. Studies on closure of the ductus arteriosus. XII. *In utero* effect of indomethacin and sodium salicylate in rats and rabbits. *Prostaglandins* 9(4):585-96.

Shen, W.W., A.G. Santi, and F.N. Bruscato. 1976. Effect of nonionic surfactants on percutaneous absorption of salicylic acid and sodium salicylate in the presence of dimethyl sulfoxide. *J Pharm Sci* 65(12):1780-3.

Shen, J., S. Wanwimolruk, R.D. Purves, E.G. McQueen, and M.S. Roberts. 1991. Model representation of salicylate pharmacokinetics using unbound plasma salicylate concentrations and metabolite urinary excretion rates following a single oral dose. *J Pharmacokinet Biopharm* 19(5):575-95.

Shetty, B.V., M. Badr, and S. Melethil. 1994. Evaluation of hepatic metabolism of salicylic acid in perfused rat liver. *J Pharm Sci* 83:607-8.

Sheu, C.W., D. Salomon, J.L. Simmons, T. Sreevalsan, and E. Freese. 1975. Inhibitory effects of lipophilic acids and related compounds on bacteria and mammalian cells. *Antimicrob Agents Chemother* 7(3):349-63.

Short, C.R., C.A. Neff-Davis, L.C. Hsieh, et al. 1991. Pharmacokinetics and elimination of salicylic acid in rabbits. *J Vet Pharmacol Ther* 14(1):70-7.

Shupp, D.L. and A.. Schroeter. 1986. An unusual case of salicylate toxicity. *J Am Acad Dermatol* 15 (2 Pt 1):300-1.

Siddiqi, M. and W.A. Ritschel. 1972. pH-Effects on salicylate absorption through the intact rat skin. *Scientia Pharm* 40(3):181-9.

Silverstein, H., J.M. Bernstein, and D.G. Davies. 1967. Salicylate ototoxicity. A biochemical and electrophysiological study. *Ann Otol Rhinol Laryngol* 76:118-28.

Singh, P. and M.S. Roberts. 1993. Iontophoretic transdermal delivery of salicylic acid and lidocaine to local subcutaneous structures. *J Pharm Sci* 82(2):127-31.

Singh, P. and M.S. Roberts. 1994. Skin permeability and local tissue concentrations of nonsteroidal anti-inflammatory drugs after topical application. *J Pharmacol Exp Ther* 268(1):144-51.

Sloan, K.B., K.G. Siver, and S.A.M. Koch. 1986. The effect of vehicle on the diffusion of salicylic acid through hairless mouse skin. *J Pharm Sci* 75(8):744-9.

Sloot, W.N. and J.B.P. Gramsbergen. 1995. Detection of salicylate and its hydroxylated adducts 2,3- and 2,5-dihydroxybenzoic acids as possible indices for *in vivo* hydroxyl radical formation in combination with catechol- and indoleamines and their metabolites in cerebrospinal fluid and brain tissue. *J Neurosci Methods* 60(1-2):141-9.

Smith, M.J.., A.W. Ford-Hutchinson, J.R. Walker, and J.A. Slack. 1979. Aspirin, salicylate and prostaglandins. *Agent Actions* 9(5/6):483-7.

Smith, W.O. and D. Lyons. 1980. Metabolic acidosis associated with percutaneous absorption of salicylic acid. *J Okla State Med Assoc* 73(1):7-8.

Soyka, P.A. and L.F. Soyka. 1980. Absorption of salicylic acid. *J Am Med Assoc* 244(7):660-1.

Speer, F. 1979. Allergy to methyl salicylate. *Ann Allergy* 43(1):36-7.

Stelzer, J.M. Jr, J.L. Colaizzi, and P.J. Wurdack. 1968. Influence of dimethyl sulfoxide (DMSO) on the percutaneous absorption of salicylic acid and sodium salicylate from ointments. *J Pharm Sci* 57(10):1732-7.

Stich, H.F., M.P. Rosin, C.H, Wu, and W.D. Powrie 1981. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. *Cancer Lett* 14(3):251-60.

Stolar, M.E., G.V. Rossi, and M. Barr. 1960. The effect of various ointment bases on the percutaneous absorption of salicylates I*. Effect of type of ointment base. *J Amer Pharm Ass, Sci Ed* 49:144-7.

Stoner, G.D., M.B. Shimkin, A.J. Kniazeff, et al. 1973. Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. *Cancer Res* 3069-85.

Strakosch, E.A. 1943. Studies on ointments. II. Ointments containing salicylic acid. *Arch Dermatol Syphilol* 47:16-26.

Strom, J.G. and H.W. Jun. 1974. Gastric irritation and bleeding after drug administration. *J Pharm Sci* 63(11):1812-3.

Sugimura, T., S. Sato, M. Nagao, et al. 1976. Overlapping of carcinogens and mutagens. *Fundam Cancer Prev Proc Int Symp Princess Takamatsu Cancer Res Fund 6th*: 191-215.

Takahashi, O. and K. Hiraga. 1985. Differences in the haemorrhagic toxicity of aspirin between rats and mice. *Acta Pharmacol Toxicol (Copenh)* 56(1):6-13.

Takahashi, M. Y. Machida, and R. Marks. 1987. Measurement of turnover time of stratum corneum using dansyl chloride fluorescence. *J Soc Cosmet Chem* 38:321-331.

Tanaka, S., K. Kawashima, S. Nakaura S, et al. 1973a. Studies on the teratogenicity of food additives (3). Teratogenic effects of dietary salicylic acid in rats. *J Food Hyg Soc Jpn* 14(6):549-57.

Tanaka, S., K. Kawashima, S. Nakaura, et al. 1973b. Studies on the teratogenic effects of salicylic acid and aspirin in rats as related to fetal distribution. *Congen Anom (Senten Ijo)* 13:73-84.

Tanaka, M., N. Yanagibashi, H. Fukuda, and T. Nagai. 1980. Absorption of salicylic acid through the oral mucous membrane of hamster cheek pouch. *Chem Pharm Bull (Toyko)* 28(4):1056-61.

Täuber, U., C. Weiss, and H. Matthes. 1993. Does salicylic acid increase the percutaneous absorption of diflucortolone-21-valerate? *Skin Pharmacol* 6(4):276-81.

Taylor, J.R. and K.M. Halprin. 1975. Percutaneous absorption of salicylic acid. *Arch Dermatol* 111(6): 740-3.

Terweij-Groen, C.P., T. Vahlkamp, and J.C. Kraak. 1978. Rapid, direct determination of trace amounts of salicylic acid in deproteinized serum by means of high pressure liquid-liquid chromatography. *J Chromatogr Biomed Appl* 145:115-22

Thiessen, J.J., R.B. Salama, F. Coceani, and P. Olley 1984. Placental drug transfer in near-term ewes: Acetylsalicylic and salicylic acid. *Can J Physiol Pharmacol* 62(4):441-5

Thune, P. 1969. Allergy to wool fat. The addition of salicylic acid for patch test purposes. *Acta Derm-Venereol* 49(3):282-7.

TKL Research, Inc. 1993a. Repeated insult patch study of product no. BK0018-182 (moisturizing cream containing 2% Salicylic Acid). TKL Study No. 931016-4 dated Sept 10. Unpublished data submitted by the Procter & Gamble Company. 41 pp.[1]

.TKL Research, Inc. 1993b. Repeated insult patch study of product no. YSC002/93 (moisturizer cream containing 2% Salicylic Acid). TKL Study No. 931018-1 dated Sept 20. Unpublished data submitted by the Procter & Gamble Company. 49 pp.[1]

TKL Research, Inc. 1993c. Repeated insult patch study of product no. BK0023-069 (moisturizer lotion containing 2% Salicylic Acid). TKL Study No. 931018 dated Sept 27. Unpublished data submitted by the Procter & Gamble Company. 50 pp.[1]

TKL Research, Inc. 1998a. 21-day cumulative irritation patch study of a facial cosmetic cream containing 1.5% Salicylic Acid. Study no. 973015 dated June 22. Unpublished data submitted by the Procter and Gamble Company. 60 pp.[1]

TKL Research, Inc. 1998a. 21-day cumulative irritation patch study of a facial cosmetic cream containing 1.5% Salicylic Acid. Study no. 973015 dated June 22. Unpublished data submitted by the Procter and Gamble Company. 61 pp.[1]

TKL Research, Inc. 1998b. 21-day cumulative irritation patch study of a facial skin conditioner cream containing 1.5% Salicylic Acid and a facial skin conditioner lotion containing 0.02% Salicylic Acid. Study no. 973009 dated June 22. Unpublished data submitted by the Procter and Gamble Company. 58 pp.[1]

TKL Research, Inc. 1998c. 21-day cumulative irritation patch study of a facial cosmetic cream containing 1.5% Salicylic Acid. Study no. 973010 dated June 22. Unpublished data submitted by the Procter and Gamble Company. 61 pp.[1]

Torrado, S., S. Torrado S, and R. Cadórniga. 1994. Comparison of assay methods by second-derivative spectroscopy, colorimetry and fluorescence spectroscopy of salicylic acid in aspirin preparations with a high performance liquid chromatographic method. *J Pharm Biomed Anal* 12(3):383-7.

Treffel P. and B. Gabard. 1996. Skin penetration and sun protection factor of ultra-violet filters from two vehicles. *Pharm Res* 13(5):770-4.

Troll, M.M. and M.L. Menten. 1945. Salicylate poisoning. Report of four cases. *Am J Dis Child* (69):37-42.

United States Pharmacopeial Convention (USP). 1995a. *The United States Pharmacopeia*, 23rd edn. United States Pharmacopeial Convention, Inc., Rockville, MD 131-8, 922-3, 1395-7, 1431-2.

USP. 1995b. *The National Formulary*, 18th edn. United States Pharmacopeial Convention, Inc., Rockville, MD 2266-7.

Van Scott, E.J. and R.J. Yu. 1974. Control of keratinization with α-hydroxy acids and related compounds. I. Topical treatment of ichthyotic disorders. *Arch Dermatol* 110:586-90.

Varma, D.R. and T.L. Yue. 1984. Influence of age, sex, pregnancy and protein-calorie malnutrition on the pharmacokinetics of salicylate in rats. *Br J Pharmacol* 82(1):241-8.

Vevy Europe. 1973a. Acute (single dose) oral toxicity study of Isodecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1973b. Acute oral toxicity study (single dose) of Tridecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1973c. Acute intraperitoneal toxicity study (single dose) of Tridecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. (1973d). Acute skin irritation test of Tridecyl Salicylate. II. Evaluation of the subacute primary irritant activity on the guinea pig skin. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. (1973e). Acute skin irritation test of Tridecyl Salicylate. I. Evaluation of the acute primary irritant activity on the rabbit skin. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1973f. Acute eye irritation test (Draize test) of Isodecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1974a. Acute skin irritation test of Isodecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1974b. Acute (single dose) intraperitoneal toxicity study of of Isodecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1975a. 15-week oral toxicity study of Isodecyl Salicylate. Unpublished data submitted by CTFA. 2 pp.[1]

Vevy Europe. 1975b. 15-week oral toxicity of Tridecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Vevy Europe. 1984. *Salmonella*/mammalian microsome mutagenicity test of Isodecyl Salicylate. Unpublished data submitted by CTFA. 1 p.[1]

Viljoen, T.C., C.H. van Aswegen, and D.J. du Plessis. 1995. Influence of acetylsalicylic acid and metabolites on DU-145 prostatic cancer cell proliferation. *Oncology* 52(6):465-9.

Villari, A., N. Micali, M. Fresta, and G. Puglisi. 1994. Spectrofluorimetry at zero angle: Determination of salicylic acid in an acetylsalicylic acid pharmaceutical formulation. *Analyst* 119(7):1561-5.

von Weiss, J.F. and W.F. Lever. 1964. Percutaneous salicylic acid intoxication in psoriasis. *Arch Dermatol* 90:614-9.

Vree, T.B., E.W.J. van Ewijk-Beneken Kolmer, C.P.W.G.M. Verwey-Van Wissen, and Y.A. Hekster. 1994a. Direct gradient reversed-phase high-performance liquid chromatographic determination of salicylic acid, with the corresponding glycine and glucuronide conjugates in human plasma and urine. *J Chromatogr* 652(2): 161-70.

Vree, T.B., E.W.J. Van Ewijk-Beneken Kolmer, C.P.W.G.M. Verwey-Van Wissen, and Y.A. Hekster. 1994b. Effect of urinary pH on the pharmacokinetics of salicylic acid, with its glycine and glucuronide conjugates in human. *Int J Clin Pharmacol Ther* 32:550-8.

Walker, R.M., P.-K. Change, and R.A. Martin. 1989. Effects of salicylate on rat liver in short-term toxicity studies. *Biochem Pharmacol* 38(2):382-4.

Walter, L.J., D.F. Biggs, and R.t. Coutts. 1974. Simultaneous GLC estimation of salicylic acid and aspirin in plasma. *J Pharm Sci* 63:1754-8.

Waltman, R., V. Tricomi, E.H. Shabanah, and R. Arenas. 1973. The effect of anti-inflammatory drugs on parturition parameters in the rat. *Prostaglandins* 4:93-106.

Wang, D.-P., C.-Y. Lin, D.-L. Chu, L.-C. Change 1997 Effect of various physical/chemical properties on the transdermal delivery of cyclosporin through topical application. *Drug Dev Ind Pharm* 23(1):99-106.

Warkany, J. and E. Takacs. 1959. Experimental production of congenital malformations in rats by salicylate poisoning. *Am J Pathol* 35(2):315-3[illegible]

Washitake, M, T. Anmo, I. Tanaka, T. Arita, and M. Nakano. 1975. Percutaneous absorption of drugs IV: Percutaneous absorption of drugs from oily vehicles. *J Pharm Sci* 64(3):397-401.

Washitake, M., T. Yajima, T. Anmo, T. Arita, and R. Hori. 1973. Studies on percutaneous absorption of drugs. III. Percutaneous absorption of drugs through damaged skin. *Chem Pharm Bull* 21:2444-51.

Webb, W.K. amdW.H. Hansen. 1963. Chronic and subacute toxicology and pathology of methyl salicylate in dogs, rats, and rabbits. *Toxicol Appl Pharmacol* 5:576-87.

Weirich, E.G., J.K. Longauer, and A.H. Kirkwood. 1975. Dermatopharmacology of salicylic acid. II. Epidermal antihyperplastic effect of salicylic acid in animals. *Dermatologica* 151:321-32.

Weirich, E.G., J.K. Longauer, and A.H. Kirkwood. 1978. Effect of topical salicylic acid on animal epidermopoiesis. *Dermatologica* 156:89-96.

Wenninger, J.A. Canterbery, R.C. and G.N. McEwen Jr, eds. 2000. *International Cosmetic Ingredient Dictionary and Handbook*, 8th edn, Vols. 1-2. Washington, DC:CTFA.

Wester, R.C., J. Melendres, L. Sedik, H. Maibach, and J.E. Riviere. 1998. Percutaneous absorption of salicylic acid, theophylline, 2,4-dimethylamine, diethyl hexyl phthalic acid, and *p*-aminobenzoic acid in the isolated perfused porcine skin flap compared to man *in vivo*. *Toxicol Appl Pharmacol* 151:159-65.

Wester, R.C., P.K. Noonan, and H.I. Maibach. 1978. Effect of salicylic acid on the percutaneous absorption of hydrocortisone. *In vivo* studies in the rhesus monkey. *Arch Dermatol* 114(8):1162-4.

Wilmer, J.L., F.G. Burleson, F. Kayama, J. Kanno, and M.I. Luster. 1994. Cytokine induction in human epidermal keratinocytes exposed to contact irritants and its relation to chemical-induced inflammation in mouse skin. *J Invest Dermatol* 102(6):915-22.

Winek, C.L., W.D. Collom, and A. Nelson Voldeng. 1973. Label similarity as an indirect cause of a methyl salicylate death. *Clin Toxicol* 6(2):189-92

Wojnar, R.J., T. Hearn, and S. Starkweather 1980 Augmentation of allergic histamine release from human leukocytes by nonsteroidal anti-inflammatory-analgesic agents. *J Allergy Clin Immunol* 66(1):37-45

Woo, D.C. and R.M. Hoar. 1972. "Apparent hydronephrosis" as a normal aspect of renal development in late gestation of rats: The effect of methyl salicylate. *Teratology* 6:191-6.

Woodford, C.M., D. Henderson, and R.P. Hamernik. 1978. Effects of combinations of sodium salicylate and noise on the auditory threshold. *Ann Otol Rhino Laryngol* 87:117-27.

Wooles, W.R., J.F. Borzelleca, and G.W. Branham, Jr. 1967. Effect of acute and prolonged salicylate administration on liver and plasma triglyceride levels and diet-induced hypercholesterolemia. *Toxicol Appl Pharmacol* 10:1-7.

Wurster, D.E. and S.F. Kramer. 1961. Investigation of some factors influencing percutaneous absorption. *J Pharm Sci* 50:288-93.

Yankell, S.L. 1972. Chapter XXXII. The effects of various vehicles on absorption rates in skin. In: Montagna, W., E.J. Van Scott, and R.B. Stoughton, eds., *Advances in Biology of Skin*. New York:Appleton-Century, 511-22.

Yano, T., T. Kanetake, M. Saita, and K. Noda. 1991. Effect of *l*-menthol and *dl*-camphor on the penetration and hydrolysis of methyl salicylate in hairless mouse skin. *J Pharmacobio-Dyn* 14:663-9.

Yokoyama, A, F. Takakubo, K. Eto, et al. 1984. Teratogenicity of aspirin and its metabolite, salicylic acid, in cultured rat embryos. *Res Commun Chem Pathol Pharmacol* 46(1):77-91.

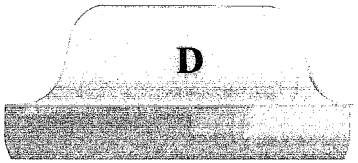
Yoshikawa, T., Y. Sugiyama, Y. Sawada, T. Iga, and M. Hanano. 1984. Effect of pregnancy on tissue distribution of salicylate in rats. *Drug Metab Disp* 12(4):500-5.

Zecchi, V., L. Rodriguez, M. Cini, and V. Viti. 1978. Formulation parameters, skin permeability and drug penetration. *Farmaco Ed Prat* 33:34-40.

Zetterberg, G. 1979. Mechanism of the lethal and mutagenic effects of phenoxyacetic acids in *Saccharomyces cerevisiae*. *Mutat Res* 60(3):291-300.

Zheng, J.L. and W.-Q. Gao. 1996. Differential damage to auditory neurons and hair cells by ototoxins and neuroprotection by specific neurotrophins in rat cochlear organotypic cultures. *Eur J Neurosci* 8(9):1897-1905.

Zhu D.X., J.L. Zhao, L. Mo, and H.L. Li. 1997. Drug allergy: Identification and characterization of IgE-reactivities to aspirin and related compounds. *J Invest Allergol Clin Immunol* 7(3):160-8.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SPONTANEOUS REPORTING SYSTEM
DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE
BRIEF DESCRIPTION WITH CAVEATS OF SYSTEM
JANUARY 30, 1996

IMPORTANT INFORMATION:

THE FILE NAMING CONVENTION FOR THE ASCII METHOD OF FOI DISTRIBUTION HAS BEEN CHANGED TO ALLOW THE DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE TO MORE QUICKLY RESPOND TO FOI REQUESTS FROM THE SPONTANEOUS REPORTING SYSTEM.

THE NEW NAMING CONVENTION WILL BE IN THE FORMAT AA######.FOI. WHERE "AA" ARE THE FIRST TWO LETTERS OF THE FILENAMES THAT WERE PREVIOUSLY USED AND "######" ARE NUMBERS USED TO SPECIFY A UNIQUE FILENAME FOR EACH FOI REQUEST. FOR EXAMPLE, THE FILE DEMO.FOI WOULD NOW BE REPRESENTED AS DE999999.FOI. THE ONLY EXCEPTIONS TO THIS RULE ARE THE README.FOI AND README2.FOI FILES. THE README.FOI FILE WILL NOW BE REPRESENTED AS RM999999.FOI AND THE README2.FOI FILE WILL BE REPRESENTED AS R2999999.FOI.

THE SPONTANEOUS REPORTING SYSTEM FOR THE DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE HAS BEEN REPROGRAMMED TO TAKE ADVANTAGE OF UP-TO-DATE METHODS FOR DATA ENTRY AND DATABASE DESIGN. DUE TO THIS REPROGRAMMING, CHANGES HAVE BEEN MADE TO THE NUMBER OF FILES AND THE LOCATION OF DATA CONTAINED IN THESE FILES. THE ORIGINAL FORMAT WAS MAINTAINED AS CLOSELY AS POSSIBLE. THESE CHANGES INCLUDE:

1) THE IMAGE ID FOR THE INITIAL REPORT IS LISTED IN THE DEMO.FOI FILE. THE IMAGE ID'S FOR THE FOLLOWUP CASES ARE LISTED SINGLY IN THE FOLLOWUP.FOI FILE.

2) ALL THE OUTCOMES FOR THE REPORTS ARE NOW LISTED IN THE OUTCOME.FOI FILE.

3) THE REPORT SOURCES FOR THE REPORTS ARE NOW LISTED IN THE SOURCE.FOI FILE.

BACKGROUND:

THE SPONTANEOUS REPORTING SYSTEM (SRS) OF THE DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE (DES) IS A COMPUTERIZED DATA BASE OF ADVERSE REACTIONS REPORTED BY HEALTH PROFESSIONALS. THE PRESENT DATA BASE CONTAINS OVER 500,000 REPORTS COLLECTED SINCE 1969. THE SYSTEM CONTAINS ONLY ADVERSE REACTIONS DETECTED AND REPORTED AFTER MARKETING OF THE DRUG. THE PRIMARY PURPOSE FOR MAINTAINING THE DATA BASE IS TO SERVE AS AN EARLY WARNING OR SIGNALING SYSTEM FOR ADVERSE DRUG REACTIONS NOT DETECTED DURING PREMARKET TESTING.

THE SRS DEPENDS ON A HEALTH PROFESSIONAL'S DETECTING A NEW CLINICAL EVENT, ATTRIBUTING THE APPEARANCE OF THE CLINICAL EVENT TO THE ADMINISTRATION OF A DRUG AND REPORTING THAT CLINICAL EVENT TO A DRUG COMPANY OR THE FDA.

THE HEALTH PROFESSIONAL MAY CHOOSE TO REPORT THE ADVERSE REACTION TO A DRUG FIRM, WHO MUST, BY LAW, REPORT TO THE FDA. NINETY PERCENT OF DES'S REPORTS ARE RECEIVED FROM DRUG MANUFACTURERS. DES RECEIVES THE REMAINING TEN PERCENT DIRECTLY FROM OTHER REPORTER(S) (I.E., HEALTH PROFESSIONALS AND CONSUMERS).

DATA FROM ALL REPORTS ARE ENTERED INTO THE DES ADVERSE DRUG REACTION DATABASE AND THE REPORT IMAGES ARE SCANNED INTO AN ELECTRONIC FILING SYSTEM (EFS).

DES HAS SWITCHED FROM MICROFILMING REPORTS TO AN ELECTRONIC FILING SYSTEM FOR

SEVERAL REASONS:

1) A REPORT AND ALL OF ITS FOLLOWUPS WILL BE GROUPED TOGETHER UNDER THE CONTROL NUMBER FOR THE ORIGINAL REPORT AND CAN BE VIEWED EASILY BY DES STAFF MEMBERS.

2) BROADER SEARCHES MAY BE PERFORMED ON THE INFORMATION CONTAINED WITHIN THE REPORTS.

3) DES WILL BE ABLE TO PROVIDE FOI REQUESTORS WITH CLEARER, MORE READABLE COPIES OF REPORTS.

THE TERM "MICROFILM ID NUMBER" WILL NO LONGER BE USED. THE CORRECT TERM IS "IMAGE ID NUMBER".

SOME CHANGES HAVE BEEN MADE TO THE FOI REPORTS BECAUSE OF REQUESTED CHANGES AND THE SWITCH TO AN ELECTRONIC FILING SYSTEM.

1) THE REPORT TYPE FIELD HAS BEEN ADDED TO THE DEMO.FOI FILE. (SEE THE DEFINITIONS SECTION).
2) THE DRUG MANUFACTURER HAS BEEN ADDED TO THE DRUG.FOI FILE.
3) ALL CONTROL NUMBERS ARE NOW PRECEEDED BY A "C" WHICH SHOULD BE INCLUDED AS PART OF THE CONTROL NUMBER WHEN REQUESTING COPIES OF REPORTS.
4) ALL IMAGE ID NUMBERS ARE NOW PRECEEDED BY A "M" WHICH SHOULD BE INCLUDED AS PART OF THE IMAGE ID NUMBER WHEN REQUESTING COPIES OF REPORTS.

WHEN REQUESTS ARE SUBMITTED FOR COPIES OF REPORTS, BOTH THE CONTROL NUMBER AND THE IMAGE ID NUMBER SHOULD BE LISTED IN TABULAR FORMAT IN ASCENDING IMAGE ID NUMBER ORDER AS SHOWN IN THE EXAMPLE BELOW,

CONTROL #	IMAGE ID #
C12345678	M87654321
C23456789	M98765432
C11111111	M99999999
.	.
.	.
.	.

CAVEATS:

THERE ARE IMPORTANT THINGS TO REMEMBER WHEN REVIEWING OR ANALYZING DATA FROM THE SPONTANEOUS REPORTING SYSTEM.

1. FOR ANY GIVEN REPORT, THERE IS NO CERTAINTY THAT THE SUSPECTED DRUG CAUSED THE REACTION. THIS IS BECAUSE PHYSICIANS ARE ENCOURAGED TO REPORT SUSPECTED REACTIONS. THE EVENT MAY HAVE BEEN RELATED TO THE UNDERLYING DISEASE FOR WHICH THE DRUG WAS GIVEN TO CONCURRENT DRUGS BEING TAKEN, OR MAY HAVE OCCURRED BY CHANCE AT THE SAME TIME THE SUSPECTED DRUG WAS TAKEN.

2. ACCUMULATED CASE REPORTS CANNOT BE USED TO CALCULATE INCIDENCE OR ESTIMATES OF DRUG RISK.

3. NUMBERS FROM THESE DATA MUST BE CAREFULLY INTERPRETED AS REPORTING RATES AND NOT OCCURRENCE RATES. TRUE INCIDENCE RATES CANNOT BE DETERMINED FROM THIS DATA BASE. COMPARISONS OF DRUGS CANNOT BE MADE FROM THESE DATA.

USE OF ADVERSE DRUG REACTION ASCII FILES

REPORTS FROM THE SPONTANEOUS REPORTING SYSTEM OF THE DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD 20857

THE ADVERSE REACTION INFORMATION REQUESTED IS SUPPLIED IN NINE FILES:

1) README.FOI - THIS FILE WHICH DESCRIBES THE FILES RECEIVED.
(NEW NAMING CONVENTION - RM######.FOI)

2) README2.FOI - LIST OF DRUGS INCLUDED AND DATE OF THIS REQUEST.
(NEW NAMING CONVENTION - R2######.FOI)

3) DEMO.FOI, WHICH CONTAINS INFORMATION ON DEMOGRAPHIC AND ADMINISTRATIVE INFORMATION AND THE INITIAL REPORT IMAGE ID.
(NEW NAMING CONVENTION - DE######.FOI)

4) DRUG.FOI, WHICH CONTAINS DRUG INFORMATION ON THE CASE REPORTS, AS MANY AS 5 PER CASE.
(NEW NAMING CONVENTION - DR######.FOI)

5) REACT.FOI, WHICH CONTAINS REACTION INFORMATION ON THE REPORTS, AS MANY AS 4 PER CASE.
(NEW NAMING CONVENTION - RE######.FOI)

6) OUTCOME.FOI, WHICH CONTAINS PATIENT OUTCOME INFORMATION ON THE REPORTS.
(NEW NAMING CONVENTION - OU######.FOI)

7) SOURCE.FOI, WHICH CONTAINS INFORMATION ON THE SOURCE OF THE REPORTS.
(NEW NAMING CONVENTION - SO######.FOI)

8) FOLLOWUP.FOI, WHICH CONTAINS IMAGE ID'S FOR FOLLOWUP REPORTS.
(NEW NAMING CONVENTION - FO######.FOI)

9) COMMENTS.FOI, WHICH CONTAINS COMMENTS ON INDIVIDUAL CASES. THE COMMENTS LISTED IN THIS FILE ARE COMMENTS ENTERED AFTER MARCH 1, 1994 ONLY. IF NONE OF THE CASES HAVE COMMENTS ENTERED AFTER MARCH 1, 1994 THIS FILE WILL NOT BE CREATED AT ALL. COMMENTS FOR ONE REPORT MAY OCCUPY SEVERAL LINES IN THE FILE. EACH LINE OF THE COMMENT IS PRECEEDED BY THE CORRESPONDING CONTROL NUMBER.
(NEW NAMING CONVENTION - CO######.FOI

DEFINITIONS

CONTROL NUMBER AN EIGHT DIGIT UNIQUE NUMBER ASSIGNED SEQUENTIALLY BY THE

FDA COMPUTER FOR INTERNAL PROCESSING AND IDENTIFICATION

DAILY DOSE	QUANTITY OF DRUG ADMINISTERED IN 24-HOUR PERIOD.
UNITS	MODIFIES THE DAILY DOSE WITH UNITS OF MEASUREMENT (E.G., MG, IU, ML, ETC.)
SUSPECT DRUG(S)	THE DRUG(S) THAT THE INITIAL REPORTER DEEMED MOST LIKELY TO BE ASSOCIATED WITH THE REACTION(S). "OTHER" DRUG(S) ARE CONCOMITANT ('S' FOR SUSPECT, 'O' FOR OTHER).
ROUTE ADM	ROUTE OF ADMINISTRATION OF THE DRUG(S) (E.G., IV, PO, TOP, ETC.)
DURATION THERP	NUMBER OF DAYS DRUG WAS USED
AGE	AGE IN YEARS. FOR INFANTS MONTHS MAY BE USED. IF SO, THE NUMBER OF MONTHS WILL BE PRECEDED BY AN "M" (E.G., 043 = 43 YEARS OLD; M07 = 7 MONTHS OLD)
SEX	M = MALE F = FEMALE U = UNKNOWN OR NOT STATED
PATIENT OUTCOME	THE RESULTS OF THE ADVERSE REACTION AS IDENTIFIED ON THE 1639/3500 REPORTING FORM. DIED, RESULTED IN SEVERE OR PROLONGED DISABILITY, RESULTED IN OR PROLONGED HOSPITALIZATION, TREATED WITH A PRESCRIPTION DRUG AND RECOVERED ARE THE POTENTIAL CHOICES. IF NO OUTCOME, IS MARKED NONE.
REACTION	THE SUSPECTED REACTION(S) CODED FROM FDA'S CODING SYMBOLS FOR A THESAURUS OF STANDARD ADVERSE REACTION TERMS
FOLLOWUP IMAGE ID	THE IMAGE ID NUMBERS ASSIGNED TO REPORT FOLLOWUPS. ** NOTE ** THERE IS NO LIMIT ON THE NUMBER OF FOLLOWUP ********** IMAGE ID'S FOR AND INDIVIDUAL REPORT.
COMMENTS	COMMENTS ENTERED FOR INDIVIDUAL REPORTS WHICH PROVIDE MORE DETAILS CONCERNING THE INCIDENT. COMMENTS ARE NOT ENTERED FOR ALL REPORTS. ONLY COMMENTS ENTERED AFTER MARCH 1, 1994 WILL BE PRINTED IN THE FOI REPORT.
REPORT TYPE	THE TYPE OF REPORT SUMITTED (SEE TABLE BELOW).

REPORT TYPE	DESCRIPTION
I	INDIVIDUAL
M	MANUFACTURER
P	PERIODIC

GENERAL SOURCE CODE	DESCRIPTION
M	MANUFACTURER
O	OTHER

OUTCOME CODE	DESCRIPTION
CON	CONGENITAL ANOMALY
DIE	DIED
DIS	DISABLED
HOS	HOSPITALIZED
INT	REQUIRED INTERVENTION TO PREVENT PERMANENT DAMAGE
LIF	LIFE-THREATENING
OTH	OTHER
NON	NONE
REC	RECOVERED
RXD	TREATED WITH RX DRUG

REPORT SOURCE CODE	DESCRIPTION
CON	CONSUMER
FOR	FOREIGN
HLT	HEALTH PROFESSIONAL
LIT	LITERATURE
STU	STUDY

SPONTANEOUS REPORTING SYSTEM - SEPTEMBER 1988

Structure of Files

1) DEMOGRAPHIC FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number (preceeded by 'C')
AGE	10 - 12	Age in years or months(preceded by 'M')
SEX	13	Sex of patient (F, M or U)
GEOGRAPHIC LOCATION	14 - 17	States (2-character) or Countries (4 char)
DATE OF BIRTH	18 - 28	DD-MMM-YYYY
ACCESSION YEAR	29 - 32	Year of receipt of report (YYYY)
ACCESSION MONTH	33 - 34	Month of receipt of report (MM)
DATE OF RECEIPT BY FDA	35 - 45	DD-MMM-YYYY
GENERAL SOURCE CODE	46 - 47	2 character code (See above table)
MANUFACTURER CONTROL NO.	48 - 67	Mfr. control no. on FDA-1639 and Mfr. report number on FDA-3500
INITIAL IMAGE ID NUMBER	68 - 76	Image id number of initial report (preceeded by 'M')
REPORT TYPE	77	The type of report submitted

2) DRUG FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number
DRUG NAME	10 - 49	
SUSPECT STATUS	50	
DAILY DOSAGE	* 52 - 62	Total dose in 24 hours

UNITS	63 - 66	
ROUTE OF ADMINISTRATION	67 - 70	
MANUFACTURER	71 - 85	
START DATE OF DRUG	86 - 96	DD-MMM-YYYY
STOP DATE OF DRUG	97 - 107	DD-MMM-YYYY

3) REACTION FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number
COSTART	10 - 30	COSTART terminology
REACTION ONSET DATE	31 - 41	DD-MMM-YYYY

4) OUTCOME FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number
OUTCOME	10 - 24	Patient outcome

5) SOURCE FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number
REPORT SOURCE	10 - 24	Source of the report

6) FOLLOWUP FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number of initial report
FOLLOWUP IMAGE ID	10 - 18	Followup image id number for report

7) COMMENTS FILE

FIELD	LOCATION IN FILE	
CONTROL NUMBER	1 - 9	Unique FDA sequentially assigned number of initial report
COMMENTS	10 - 132	Comments on the individual report

* Indicates fields which are numeric datatypes. These fields are preceeded by a space which is alotted for the sign (+/-) of the numeric data. Field positions listed are actual positions excluding the space for the sign.

ADVERSE DRUG REACTIONS: SALICYLIC ACID

SPONTANEOUS REPORTING SYSTEM

DIVISION OF EPIDEMIOLOGY AND SURVEILLANCE

1969 -1997

DrugName	Co...	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec...	Source	ManufacControl	InitialImageId	RepType	FollowupID	Comments	Outcome	C...	Onset	RptCd
SALICYLIC ACID	C0000...	O							002	M	1970	07	01-Ju...	M		M00017527				REC	MARROW DEPRESS	01-Feb-70	FOR
SALICYLIC ACID	C00026471	S			TOP		03-Dec-69	03-Dec-69	017	F	1970	01	01-Jan-70	O		M00026471	I			REC	DERM CONTACT	03-Dec-69	
SALICYLIC ACID	C00075477	O			TOP				024	M	1975	09	01-Sep-75	O		M00075477	I				DERM CONTACT	08-Sep-75	
SALICYLIC ACID	C00081338	S			TOP		14-May-75	18-May-75		F	1975	09	01-Sep-75	O		M00081338	I			REC	DERM CONTACT	18-May-75	
SALICYLIC ACID	C00118684	O			TOP				033	M	1981	05	01-May-81	M		M00118684	M			REC	DYSPNEA	11-Feb-81	
SALICYLIC ACID	C00118684	O			TOP				033	M	1981	05	01-May-81	M		M00118684	M			REC	PRURITUS	11-Feb-81	
SALICYLIC ACID	C00118684	O			TOP				033	M	1981	05	01-May-81	M		M00118684	M			REC	URTICARIA	11-Feb-81	
SALICYLIC ACID	C00121916	S			TOP		01-Jul-81	01-Jul-81	049	M	1981	09	01-Sep-81	O		M00121916	I				INFECT	01-Jul-81	CON
SALICYLIC ACID	C00152493	O							069	M	1983	02	11-Feb-83	M	00EL8293	M00152493	M	M00343484		REC	MANIC REACT		
SALICYLIC ACID	C00152493	O							069	M	1983	02	11-Feb-83	M	00EL8293	M00152493	M	M00343484		REC	PERSON DIS		
SALICYLIC ACID	C00160844	O							034	M	1981	06	19-Jun-81	M	10049B02	M00160844				REC	DYSPNEA	11-Feb-81	
SALICYLIC ACID	C00160844	O							034	M	1981	06	19-Jun-81	M	10049B02	M00160844				REC	PRURITUS	11-Feb-81	
SALICYLIC ACID	C00160844	O							034	M	1981	06	19-Jun-81	M	10049B02	M00160844				REC	URTICARIA		
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	EDEMA LUNG	09-Dec-85	FOR
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	EDEMA LUNG	09-Dec-85	STU
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	HEART FAIL	09-Dec-85	FOR
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	HEART FAIL	09-Dec-85	STU
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	RESPIRAT DIS	09-Dec-85	FOR
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	RESPIRAT DIS	09-Dec-85	STU
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	SEPSIS	09-Dec-85	FOR
SALICYLIC ACID	C00383994	O							044	F	1986	02	25-Feb-86	M	8600162C	M00383994	P			DIE	SEPSIS	09-Dec-85	STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	COMA		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	COMA		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	COMA		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	DEHYDRAT		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	DEHYDRAT		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	DEHYDRAT		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	FEVER		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	FEVER		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	FEVER		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	VOMIT		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	VOMIT		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		HOS	VOMIT		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	COMA		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	COMA		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	COMA		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	DEHYDRAT		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	DEHYDRAT		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	DEHYDRAT		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	FEVER		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	FEVER		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	FEVER		STU
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	VOMIT		FOR
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	VOMIT		HLT
SALICYLIC ACID	C00389824	O							M11	F	1986	03	28-Mar-86	M	86030699A	M00389824	M	M00412997		REC	VOMIT		STU
SALICYLIC ACID	C00395564	O							048	M	1986	03	14-Mar-86	M	851144	M00395564	P				HAIR DIS	12-Nov-85	HLT
SALICYLIC ACID	C00395565	S							052	F	1986	03	14-Mar-86	M	851147	M00395565	P				HAIR DIS	22-Nov-85	HLT

DrugName	Ge	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec	Source	ManufacContrl	InitialImageId	RepType	FollowupID	Comments	Outcome	PT	OnsDt	RxCd
SALICYLIC ACID	C00417439	O								U	1986	09	09-Sep-86	M	FDT02929	M00417439	M			DIS	ANOMALY CONGEN		FOR
SALICYLIC ACID	C00417439	O								U	1986	09	09-Sep-86	M	FDT02929	M00417439	M			DIS	ANOMALY CONGEN		HLT
SALICYLIC ACID	C00417439	O								U	1986	09	09-Sep-86	M	FDT02929	M00417439	M			DIS	ANOMALY CONGEN		LIT
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	PAIN ABDO	01-Oct-85	FOR
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	PAIN ABDO	01-Oct-85	HLT
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	PAIN ABDO	01-Oct-85	STU
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	VOMIT	01-Oct-85	FOR
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	VOMIT	01-Oct-85	HLT
SALICYLIC ACID	C00423256	O							003	M	1986	10	10-Oct-86	M	86020023A	M00423256	P			HOS	VOMIT	01-Oct-85	STU
SALICYLIC ACID	C00428764	O							009	F	1986	10	10-Oct-86	M	85080205A	M00428764	P				LE SYND	03-Aug-85	FOR
SALICYLIC ACID	C00428764	O							009	F	1986	10	10-Oct-86	M	85080205A	M00428764	P				LE SYND	03-Aug-85	HLT
SALICYLIC ACID	C00459242	O							040	M	1987	04	03-Apr-87	M	862134001	M00459242	P			NON	SERUM IRON INC	04-Oct-86	HLT
SALICYLIC ACID	C00459242	O							040	M	1987	04	03-Apr-87	M	862134001	M00459242	P			REC	SERUM IRON INC	04-Oct-86	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	ALOPECIA	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	ALOPECIA	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	FIBRO LUNG	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	FIBRO LUNG	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	GASTRITIS	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	GASTRITIS	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	VEIN VARICOSE	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			HOS	VEIN VARICOSE	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	ALOPECIA	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	ALOPECIA	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	FIBRO LUNG	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	FIBRO LUNG	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	GASTRITIS	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	GASTRITIS	14-Jun-82	HLT
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	VEIN VARICOSE	14-Jun-82	FOR
SALICYLIC ACID	C00465740	O							053	F	1987	05	18-May-87	M	860312975001	M00465740	M			RXD	VEIN VARICOSE	14-Jun-82	HLT
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	HEART ARREST	01-Aug-87	FOR
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	HEART ARREST	01-Aug-87	HLT
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	HEART ARREST	01-Aug-87	STU
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	INFARCT MYOCARD	01-Aug-87	FOR
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	INFARCT MYOCARD	01-Aug-87	HLT
SALICYLIC ACID	C00488059	O							056	M	1987	09	28-Sep-87	M	8702624	M00488059	M			DIE	INFARCT MYOCARD	01-Aug-87	STU
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	HEPATITIS	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	HEPATITIS	27-Jun-87	HLT
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	PSORIASIS	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	PSORIASIS	27-Jun-87	HLT
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	REACT AGGRAV	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			HOS	REACT AGGRAV	27-Jun-87	HLT
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	HEPATITIS	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	HEPATITIS	27-Jun-87	HLT
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	PSORIASIS	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	PSORIASIS	27-Jun-87	HLT
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	REACT AGGRAV	27-Jun-87	FOR
SALICYLIC ACID	C00502607	O							029	F	1987	12	04-Dec-87	M	870500275001	M00502607	M			RXD	REACT AGGRAV	27-Jun-87	HLT

DrugName	Con	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec'd	Source	ManufacCont#	InitialImageId	RepType	Followup ID	Comments	Outcome	Cos	Onset	RptCd
SALICYLIC ACID	C005106	S			TOP				079	F	1988	02	09-Feb-88	O		M00510632	I			NON	APPLICAT SITE REACT	10-Dec-87	HLT
SALICYLIC ACID	C00510632	S			TOP				079	F	1988	02	09-Feb-88	O		M00510632	I			NON	ULCER SKIN	10-Dec-87	HLT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	KIDNEY FAIL ACUTE		FOR
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	KIDNEY FAIL ACUTE		HLT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	KIDNEY FAIL ACUTE		LIT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	LIVER DAMAGE		FOR
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	LIVER DAMAGE		HLT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	LIVER DAMAGE		LIT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	OVERDOSE ACCID		FOR
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	OVERDOSE ACCID		HLT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	OVERDOSE ACCID		LIT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	VASC DIS		FOR
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	VASC DIS		HLT
SALICYLIC ACID	C00531529	O							051	M	1988	07	07-Jul-88	M	TLBD8803250F	M00531529	M			HOS	VASC DIS		LIT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	CREATININE INC		FOR
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	CREATININE INC		HLT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	CREATININE INC		LIT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	KIDNEY FAIL ACUTE		FOR
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	KIDNEY FAIL ACUTE		HLT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	KIDNEY FAIL ACUTE		LIT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	VASC DIS		FOR
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	VASC DIS		HLT
SALICYLIC ACID	C00531530	O							054	M	1988	07	07-Jul-88	M	TLBD8803250E	M00531530	M			HOS	VASC DIS		LIT
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	BUN INC	02-May-88	FOR
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	BUN INC	02-May-88	HLT
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	CREATININE INC	02-May-88	FOR
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	CREATININE INC	02-May-88	HLT
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	FEVER	02-May-88	FOR
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	FEVER	02-May-88	HLT
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	KIDNEY FAIL	02-May-88	FOR
SALICYLIC ACID	C00531905	O							084	M	1988	07	07-Jul-88	M	ARR44979	M00531905	M	M00567088		DIS	KIDNEY FAIL	02-May-88	HLT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	CREATININE INC		FOR
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	CREATININE INC		HLT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	CREATININE INC		LIT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	KIDNEY FAIL ACUTE		FOR
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	KIDNEY FAIL ACUTE		HLT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	KIDNEY FAIL ACUTE		LIT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	OVERDOSE INTENT		FOR
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	OVERDOSE INTENT		HLT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	OVERDOSE INTENT		LIT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	VASC DIS		FOR
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	VASC DIS		HLT
SALICYLIC ACID	C00531927	O							039	M	1988	07	07-Jul-88	M	TLBD8803250D	M00531927	M			HOS	VASC DIS		LIT
SALICYLIC ACID	C00535050	O							044	M	1988	08	03-Aug-88	M	880400060001	M00535050	M			DIS	ANOMALY CONGEN		FOR
SALICYLIC ACID	C00535050	O							044	M	1988	08	03-Aug-88	M	880400060001	M00535050	M			DIS	ANOMALY CONGEN		HLT
SALICYLIC ACID	C00605843	O								U	1989	09	11-Sep-89	M	WAES89080663	M00605843	M			HOS	AGRANULOCYTOSIS	01-Feb-89	FOR
SALICYLIC ACID	C00605843	O								U	1989	09	11-Sep-89	M	WAES89080663	M00605843	M			HOS	INFECT	01-Feb-89	FOR

DrugName	Con	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec	Source	ManufacCont#	InitialMapId	RepType	FollowUp ID	Comments	Outcome	PT	Death	RptCtr
SALICYLIC ACID	C00600	O								U	1989	09	11-Sep-	M	WAES89080663	M00605843	M			HOS	PHARYNGITIS	01-Feb-89	FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	ANAPHYL		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	ANAPHYL		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	FIBRILLAT VENT		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	FIBRILLAT VENT		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	HYPOTENS		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	HYPOTENS		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	HYPOXIA		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		DIE	HYPOXIA		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	ANAPHYL		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	ANAPHYL		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	FIBRILLAT VENT		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	FIBRILLAT VENT		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	HYPOTENS		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	HYPOTENS		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	HYPOXIA		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		HOS	HYPOXIA		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	ANAPHYL		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	ANAPHYL		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	FIBRILLAT VENT		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	FIBRILLAT VENT		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	HYPOTENS		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	HYPOTENS		HLT
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	HYPOXIA		FOR
SALICYLIC ACID	C00612544	O							068	M	1989	10	04-Oct-89	M	G0002671	M00612544	M	M00616636		RXD	HYPOXIA		HLT
SALICYLIC ACID	C00614836	S			TOP		27-Mar-89	28-Mar-89	014	F	1989	08	22-Aug-89	O		M00614836	I			RXD	DERM EXFOL	27-Mar-89	HLT
SALICYLIC ACID	C00614836	S			TOP		27-Mar-89	28-Mar-89	014	F	1989	08	22-Aug-89	O		M00614836	I			RXD	EDEMA	27-Mar-89	HLT
SALICYLIC ACID	C00614836	S			TOP		27-Mar-89	28-Mar-89	014	F	1989	08	22-Aug-89	O		M00614836	I			RXD	SKIN DISCOLOR	27-Mar-89	HLT
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	GI DIS	14-Jun-82	FOR
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	GI DIS	14-Jun-82	HLT
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	HEM ESOPH	14-Jun-82	FOR
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	HEM ESOPH	14-Jun-82	HLT
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	HYPERTENS	14-Jun-82	FOR
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	HYPERTENS	14-Jun-82	HLT
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	LIVER CIRRHO	14-Jun-82	FOR
SALICYLIC ACID	C00650290	O							053	F	1990	03	28-Mar-90	M	850312975001	M00650290	M	M00657940		HOS	LIVER CIRRHO	14-Jun-82	HLT
SALICYLIC ACID	C00674251	O							053	M	1990	06	26-Jun-90	M	WAES90060584	M00674251	M			DIS	GANGRENE PERIPH	10-Apr-90	FOR
SALICYLIC ACID	C00674251	O							053	M	1990	06	26-Jun-90	M	WAES90060584	M00674251	M			DIS	GANGRENE PERIPH	10-Apr-90	HLT
SALICYLIC ACID	C00674251	O							053	M	1990	06	26-Jun-90	M	WAES90060584	M00674251	M			DIS	VASC DIS PERIPH	10-Apr-90	FOR
SALICYLIC ACID	C00674251	O							053	M	1990	06	26-Jun-90	M	WAES90060584	M00674251	M			DIS	VASC DIS PERIPH	10-Apr-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	EDEMA LUNG	01-Mar-90	FOR
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	EDEMA LUNG	01-Mar-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	HYPERKALEM	01-Mar-90	FOR
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	HYPERKALEM	01-Mar-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	INFARCT MYOCARD	01-Mar-90	FOR
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			DIE	INFARCT MYOCARD	01-Mar-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	EDEMA LUNG	01-Mar-90	FOR

DrugName	Cor	Suspect	D Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec	Source	ManufacCont	InitialImageId	RepType	FollowupID	Comments	Outcome	Co	Onset	RptCod
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	EDEMA LUNG	01-Mar-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	HYPERKALEM	01-Mar-90	FOR
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	HYPERKALEM	01-Mar-90	HLT
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	INFARCT MYOCARD	01-Mar-90	FOR
SALICYLIC ACID	C00704983	O							087	F	1990	11	21-Nov-90	M	WAES90110732	M00704983	M			HOS	INFARCT MYOCARD	01-Mar-90	HLT
SALICYLIC ACID	C00705627	O							083	M	1990	11	28-Nov-90	M	900458P02M1	M00705627	M			HOS	ANURIA	21-Aug-90	FOR
SALICYLIC ACID	C00705627	O							083	M	1990	11	28-Nov-90	M	900458P02M1	M00705627	M			HOS	ANURIA	21-Aug-90	HLT
SALICYLIC ACID	C00705627	O							083	M	1990	11	28-Nov-90	M	900458P02M1	M00705627	M			HOS	CREATININE INC	21-Aug-90	FOR
SALICYLIC ACID	C00705627	O							083	M	1990	11	28-Nov-90	M	900458P02M1	M00705627	M			HOS	CREATININE INC	21-Aug-90	HLT
SALICYLIC ACID	C00720635	O							072	M	1991	01	23-Jan-91	M	901101SK948	M00720635	P	M00742270		RXD	DIARRHEA	28-Oct-90	HLT
SALICYLIC ACID	C00720635	O							072	M	1991	01	23-Jan-91	M	901101SK948	M00720635	P	M00742270		RXD	PAIN ABDO	28-Oct-90	HLT
SALICYLIC ACID	C00725784	O							062	F	1991	02	20-Feb-91	M	NL91014540A	M00725784	M			HOS	HEADACHE	11-Jan-90	FOR
SALICYLIC ACID	C00725784	O							062	F	1991	02	20-Feb-91	M	NL91014540A	M00725784	M			HOS	HEADACHE	11-Jan-90	HLT
SALICYLIC ACID	C00725784	O							062	F	1991	02	20-Feb-91	M	NL91014540A	M00725784	M			HOS	HEADACHE	11-Jan-90	STU
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	SALICYLISM	21-Jan-91	FOR
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	SALICYLISM	21-Jan-91	HLT
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	THINKING ABNORM		FOR
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	THINKING ABNORM		HLT
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	TINNITUS	21-Jan-91	FOR
SALICYLIC ACID	C00733711	O							027	M	1991	03	14-Mar-91	M	910400045001	M00733711	M			HOS	TINNITUS	21-Jan-91	HLT
SALICYLIC ACID	C00748355	O							084	M	1991	04	23-Apr-91	M	911305001	M00748355	M	M00789161		DIE	PERITONITIS	07-May-90	FOR
SALICYLIC ACID	C00748355	O							084	M	1991	04	23-Apr-91	M	911305001	M00748355	M	M00789161		DIE	PERITONITIS	07-May-90	HLT
SALICYLIC ACID	C00748355	O							084	M	1991	04	23-Apr-91	M	911305001	M00748355	M	M00789161		DIE	ULCER DUODEN PER	07-May-90	FOR
SALICYLIC ACID	C00748355	O							084	M	1991	04	23-Apr-91	M	911305001	M00748355	M	M00789161		DIE	ULCER DUODEN PER	07-May-90	HLT
SALICYLIC ACID	C00775659	O							041	M	1991	09	24-Sep-91	M	910400044001	M00775659	M			HOS	APNEA	28-Jan-91	FOR
SALICYLIC ACID	C00775659	O							041	M	1991	09	24-Sep-91	M	910400044001	M00775659	M			HOS	APNEA	28-Jan-91	HLT
SALICYLIC ACID	C00775659	O							041	M	1991	09	24-Sep-91	M	910400044001	M00775659	M			HOS	STUPOR	28-Jan-91	FOR
SALICYLIC ACID	C00775659	O							041	M	1991	09	24-Sep-91	M	910400044001	M00775659	M			HOS	STUPOR	28-Jan-91	HLT
SALICYLIC ACID	C00824014	O							029	M	1992	03	13-Mar-92	M	M91126	M00824014	P				DRUG INTERACTION		HLT
SALICYLIC ACID	C00827876	O							003	M	1992	04	13-Apr-92	M	9103006	M00827876	P			NON	NO DRUG EFFECT		HLT
SALICYLIC ACID	C00827876	O							003	M	1992	04	13-Apr-92	M	9103006	M00827876	P			REC	NO DRUG EFFECT		HLT
SALICYLIC ACID	C00880702	S			TOP	CLAY-PARK			013	M	1992	09	10-Sep-92	O	SAN4360	M00880702	I			RXD	APPLICAT SITE REACT		CON
SALICYLIC ACID	C00880702	S			TOP	CLAY-PARK			013	M	1992	09	10-Sep-92	O	SAN4360	M00880702	I			RXD	PAIN		CON
SALICYLIC ACID	C00880702	S			TOP	CLAY-PARK			013	M	1992	09	10-Sep-92	O	SAN4360	M00880702	I			RXD	SKIN DIS		CON
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		DIS	ARTHRITIS RHEUMAT		FOR
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		DIS	ARTHRITIS RHEUMAT		HLT
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		DIS	FIBRO LUNG		FOR
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		DIS	FIBRO LUNG		HLT
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		HOS	ARTHRITIS RHEUMAT		FOR
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		HOS	ARTHRITIS RHEUMAT		HLT
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		HOS	FIBRO LUNG		FOR
SALICYLIC ACID	C00885180	O							058	M	1992	10	02-Oct-92	M	920318353001	M00885180	M	M01404640		HOS	FIBRO LUNG		HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	HEART FAIL	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	HEART FAIL	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	KIDNEY FUNC ABNORM	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	KIDNEY FUNC ABNORM	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	MYOPATHY	01-Nov-92	FOR

DrugName	Co[illegible]	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec[illegible]	Source	ManufacContr#	InitialImageId	RepType	FollowupID	Comments	Outcome	[illegible] Co	[illegible]	[illegible]
SALICYLIC ACID	C0091[illegible]	O							062	M	1993	01	13-Jan-[illegible]	M	WAES92125560	M00911046	M	M00960374		DIE	MYOPATHY	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	SEPSIS	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIE	SEPSIS	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	HEART FAIL	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	HEART FAIL	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	KIDNEY FUNC ABNORM	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	KIDNEY FUNC ABNORM	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	MYOPATHY	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	MYOPATHY	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	SEPSIS	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		DIS	SEPSIS	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	HEART FAIL	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	HEART FAIL	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	KIDNEY FUNC ABNORM	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	KIDNEY FUNC ABNORM	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	MYOPATHY	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	MYOPATHY	01-Nov-92	HLT
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	SEPSIS	01-Nov-92	FOR
SALICYLIC ACID	C00911046	O							062	M	1993	01	13-Jan-93	M	WAES92125560	M00911046	M	M00960374		HOS	SEPSIS	01-Nov-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		HOS	AV BLOCK FD	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		HOS	ECG ABNORM	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		HOS	MIGRAINE	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		HOS	PANCREATITIS	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		RXD	AV BLOCK FD	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		RXD	ECG ABNORM	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		RXD	MIGRAINE	11-Dec-92	HLT
SALICYLIC ACID	C00940957	O							072	F	1993	03	03-Mar-93	M	WAES92120866	M00940957	M	M00953721		RXD	PANCREATITIS	11-Dec-92	HLT
SALICYLIC ACID	C01348201	S	2.00	TB	PO				088	M	1993	07	16-Jul-93	O		M01349511	I			RXD	AMNESIA	02-Nov-92	HLT
SALICYLIC ACID	C01348201	S	2.00	TB	PO				088	M	1993	07	16-Jul-93	O		M01349511	I			RXD	DYSPHAGIA	02-Nov-92	HLT
SALICYLIC ACID	C01348201	S	2.00	TB	PO				088	M	1993	07	16-Jul-93	O		M01349511	I			RXD	HALLUCIN	02-Nov-92	HLT
SALICYLIC ACID	C01348201	S	2.00	TB	PO				088	M	1993	07	16-Jul-93	O		M01349511	I			RXD	NERVOUSNESS	02-Nov-92	HLT
SALICYLIC ACID	C01350635	O							063	F	1993	07	20-Jul-93	O		M01346787	I			DIS	FIBRO LUNG	15-Apr-93	HLT
SALICYLIC ACID	C01350635	O							063	F	1993	07	20-Jul-93	O		M01346787	I			DIS	LUNG FUNC DEC	15-Apr-93	HLT
SALICYLIC ACID	C01350635	O							063	F	1993	07	20-Jul-93	O		M01346787	I			HOS	FIBRO LUNG	15-Apr-93	HLT
SALICYLIC ACID	C01350635	O							063	F	1993	07	20-Jul-93	O		M01346787	I			HOS	LUNG FUNC DEC	15-Apr-93	HLT
SALICYLIC ACID	C01367012	O							079	F	1993	09	21-Sep-93	M	935337A1440	M01449850	M			LIF	HEM CEREBR	05-Sep-90	FOR
SALICYLIC ACID	C01367012	O							079	F	1993	09	21-Sep-93	M	935337A1440	M01449850	M			LIF	HEM CEREBR	05-Sep-90	HLT
SALICYLIC ACID	C01385864	O								F	1993	11	05-Nov-93	M	930100724001	M01386973	M				ANOMALY CONGEN		FOR
SALICYLIC ACID	C01385864	O								F	1993	11	05-Nov-93	M	930100724001	M01386973	M				ANOMALY CONGEN		HLT
SALICYLIC ACID	C01385864	O								F	1993	11	05-Nov-93	M	930100724001	M01386973	M				ANOMALY CONGEN		LIT
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	DIPLOPIA	06-Sep-93	FOR
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	DIPLOPIA	06-Sep-93	HLT
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	HALLUCIN	06-Sep-93	FOR
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	HALLUCIN	06-Sep-93	HLT
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	HEADACHE	06-Sep-93	FOR
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	HEADACHE	06-Sep-93	HLT
SALICYLIC ACID	C01392789	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	VISION ABNORM	06-Sep-93	FOR

DrugName	Cor	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec	Source	ManufacContr#	InitialImageId	RepType	Followup ID	Comments	Outcome	Co	Onset	[illegible]
SALICYLIC ACID	C01392[illegible]	O								F	1993	11	24-Nov-93	M	933508001	M01399878	M			HOS	VISION ABNORM	06-Sep-93	HLT
SALICYLIC ACID	C01393341	S	2 00	TB	PO				088	M	1993	11	02-Nov-93	O		M01395907	I			RXD	AMNESIA	02-Nov-92	HLT
SALICYLIC ACID	C01393341	S	2 00	TB	PO				088	M	1993	11	02-Nov-93	O		M01395907	I			RXD	DYSPHAGIA	02-Nov-92	HLT
SALICYLIC ACID	C01393341	S	2 00	TB	PO				088	M	1993	11	02-Nov-93	O		M01395907	I			RXD	HALLUCIN	02-Nov-92	HLT
SALICYLIC ACID	C01393341	S	2 00	TB	PO				088	M	1993	11	02-Nov-93	O		M01395907	I			RXD	NERVOUSNESS	02-Nov-92	HLT
SALICYLIC ACID	C01415693	O								U	1994	02	02-Feb-94	M	930057681	M01426073	P				DRUG INTERACTION		HLT
SALICYLIC ACID	C01415693	O								U	1994	02	02-Feb-94	M	930057681	M01426073	P				DRUG LEVEL INC		HLT
SALICYLIC ACID	C01440631	O							074	M	1994	03	15-Mar-94	O		M01447875	I		LOTION	INT	PROSTAT DIS		HLT
SALICYLIC ACID	C01468756	O							047	M	1994	05	27-May-94	M	RETROVIR1014	M01471851	P		HIV(+) PATIENT	HOS	ANEMIA	09-Apr-94	HLT
SALICYLIC ACID	C01468756	O							047	M	1994	05	27-May-94	M	RETROVIR1014	M01471851	P		HIV(+) PATIENT	HOS	ANEMIA HYPOCHROM	09-Apr-94	HLT
SALICYLIC ACID	C01468756	O							047	M	1994	05	27-May-94	M	RETROVIR1014	M01471851	P		HIV(+) PATIENT	HOS	ASTHENIA	09-Apr-94	HLT
SALICYLIC ACID	C01468756	O							047	M	1994	05	27-May-94	M	RETROVIR1014	M01471851	P		HIV(+) PATIENT	HOS	MALAISE	09-Apr-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	ANGIOEDEMA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	ANGIOEDEMA	03-Oct-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	DYSPNEA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	DYSPNEA	03-Oct-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	URTICARIA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			HOS	URTICARIA	03-Oct-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	ANGIOEDEMA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	ANGIOEDEMA	03-Oct-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	DYSPNEA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	DYSPNEA	03-Oct-94	HLT
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	URTICARIA	03-Oct-94	FOR
SALICYLIC ACID	C01541352	O					01-Oct-94	03-Oct-94	043	F	1994	12	19-Dec-94	M	9412028	M01553014	M			LIF	URTICARIA	03-Oct-94	HLT
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	EDEMA PERIPH	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	EDEMA PERIPH	30-Aug-94	HLT
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	RASH	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	RASH	30-Aug-94	HLT
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	VASCULITIS	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			HOS	VASCULITIS	30-Aug-94	HLT
SALICYLIC ACID	C01544432	O							[illegible]	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	EDEMA PERIPH	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	EDEMA PERIPH	30-Aug-94	HLT
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	RASH	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	RASH	30-Aug-94	HLT
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	VASCULITIS	30-Aug-94	FOR
SALICYLIC ACID	C01544432	O							080	F	1995	01	23-Jan-95	M	HU95010817A	M01556328	M			INT	VASCULITIS	30-Aug-94	HLT
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		INITIATED FOR	HOS	EEG ABNORM	28-Mar-95	FOR
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		INITIATED FOR	HOS	EEG ABNORM	28-Mar-95	HLT
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		INITIATED FOR	HOS	SYNCOPE	23-Mar-95	FOR
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		INITIATED FOR	HOS	SYNCOPE	23-Mar-95	HLT
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		SCAN NORMALL &	HOS	EEG ABNORM	28-Mar-95	FOR
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		SCAN NORMALL &	HOS	EEG ABNORM	28-Mar-95	HLT
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		SCAN NORMALL &	HOS	SYNCOPE	23-Mar-95	FOR
SALICYLIC ACID	C01574431	O					01-Mar-95		059	M	1995	04	20-Apr-95	M	95040021	M01683344	M		SCAN NORMALL &	HOS	SYNCOPE	23-Mar-95	HLT
SALICYLIC ACID	C01575034	S	1 00	U	TOP		30-Mar-95	31-Mar-95	050	M	1995	04	11-Apr-95	O		M01589826	I			NON	APPLICAT SITE REACT	30-Mar-95	HLT
SALICYLIC ACID	C01575034	S	1 00	U	TOP		30-Mar-95	31-Mar-95	050	M	1995	04	11-Apr-95	O		M01589826	I			NON	DERM EXFOL	30-Mar-95	HLT
SALICYLIC ACID	C01575034	S	1 00	U	TOP		30-Mar-95	31-Mar-95	050	M	1995	04	11-Apr-95	O		M01589826	I			NON	PAIN	30-Mar-95	HLT

DrugName	Co	Suspect	D.Dosage	Unit	Route	Manufacturer	Start Date	Stop Date	Age	Sex	AccYr	AccMon	Rec	Source	ManufacConN	InitialImageId	RepType	Followup ID	Comments	Outcome	[illegible]	Onset	RptCd
SALICYLIC ACID	C0157[illegible]	S	1 00	U	TOP		30-Mar-95	31-Mar-95	050	M	1995	04	11-Apr-[illegible]	O		M01589826	I			NON	SKIN DISCOLOR	30-Mar-95	HLT
SALICYLIC ACID	C01658541	O								F	1995	10	25-Oct-95	M	950503107050521	M01681019	P				APPLICAT SITE REACT	28-Apr-95	CON
SALICYLIC ACID	C01658541	O								F	1995	10	25-Oct-95	M	950503107050521	M01681019	P				RASH	28-Apr-95	CON
SALICYLIC ACID	C01658541	O								F	1995	10	25-Oct-95	M	950503107050521	M01681019	P				SKIN DRY	28-Apr-95	CON
SALICYLIC ACID	C01663899	O							048	M	1995	11	08-Nov-95	M	80940184201	M01685748	P		12 5 MG/WK.	DIS	LIVER DAMAGE	15-Apr-94	HLT
SALICYLIC ACID	C01663899	O							048	M	1995	11	08-Nov-95	M	80940184201	M01685748	P		12 5 MG/WK.	DIS	LIVER FUNC ABNORM	15-Apr-94	HLT
SALICYLIC ACID	C01675761	O							049	F	1995	11	28-Nov-95	M	9502138	M01694504	P		Q12H FOR 2 DAYS.		INSOMNIA	14-Jan-95	CON
SALICYLIC ACID	C01675761	O							049	F	1995	11	28-Nov-95	M	9502138	M01694504	P		Q12H FOR 2 DAYS.		NERVOUSNESS	14-Jan-95	CON
SALICYLIC ACID	C01675761	O							049	F	1995	11	28-Nov-95	M	9502138	M01694504	P		Q12H FOR 2 DAYS.		NO DRUG EFFECT	14-Jan-95	CON
SALICYLIC ACID	C01698089	S					09-Oct-95		074	F	1996	01	24-Jan-96	O		M01719303	I			HOS	EDEMA FACE	10-Oct-95	HLT
SALICYLIC ACID	C01698089	S					09-Oct-95		074	F	1996	01	24-Jan-96	O		M01719303	I			HOS	FEVER	10-Oct-95	HLT
SALICYLIC ACID	C01698089	S					09-Oct-95		074	F	1996	01	24-Jan-96	O		M01719303	I			HOS	LEUKOCYTOSIS	10-Oct-95	HLT
SALICYLIC ACID	C01698089	S					09-Oct-95		074	F	1996	01	24-Jan-96	O		M01719303	I			HOS	RASH	10-Oct-95	HLT
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	ANEMIA	01-Oct-95	FOR
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	ANEMIA	01-Oct-95	HLT
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	DRUG INTERACTION	01-Oct-95	FOR
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	DRUG INTERACTION	01-Oct-95	HLT
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	HEM GI	01-Oct-95	FOR
SALICYLIC ACID	C01727611	S			PO	PFIZER		23-Oct-95	082	F	1996	03	22-Mar-96	M	9602869	M01751619	M		FELDENE,	HOS	HEM GI	01-Oct-95	HLT
SALICYLIC ACID	C01802311	O							026	F	1996	08	08-Aug-96	M	199603096	M01828326	P		AZELEX 9% BSA		ACNE	12-May-96	CON
SALICYLIC ACID	C01802311	O							026	F	1996	08	08-Aug-96	M	199603096	M01828326	P		AZELEX 9% BSA		APPLICAT SITE REACT	12-May-96	CON
SALICYLIC ACID	C01802311	O							026	F	1996	08	08-Aug-96	M	199603096	M01828326	P		AZELEX 9% BSA		DERM CONTACT	12-May-96	CON
SALICYLIC ACID	C01802311	O							026	F	1996	08	08-Aug-96	M	199603096	M01828326	P		AZELEX 9% BSA		REACT AGGRAV	12-May-96	CON
SALICYLIC ACID	C01810187	O							015	M	1996	08	21-Aug-96	M	960119107050161	M01836550	P		5%		RASH	09-Jan-96	CON
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	AMBLYOPIA	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	AMBLYOPIA	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	HYPOTENS POST	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	HYPOTENS POST	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	MALAISE	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	HOS	MALAISE	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	AMBLYOPIA	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	AMBLYOPIA	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	HYPOTENS POST	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	HYPOTENS POST	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	MALAISE	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	OTH	MALAISE	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	AMBLYOPIA	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	AMBLYOPIA	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	HYPOTENS POST	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	HYPOTENS POST	21-May-96	HLT
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	MALAISE	21-May-96	FOR
SALICYLIC ACID	C01817363	O					01-Apr-95		032	F	1996	09	30-Sep-96	M	71397F	M01842786	P	M01938768	HIV	REC	MALAISE	21-May-96	HLT
SALICYLIC ACID	C01944735	O							075	M	1997	05	02-May-97	M	01171997M010	M01980403	P				RASH	10-Jan-97	CON
SALICYLIC ACID	C02010722	O							022	F	1997	06	04-Jun-97	M	970160	M02058806	M		NIUM BROMIDE.	HOS	STEVENS JOHNSON SYNDROME	17-Aug-95	FOR

ADVERSE EVENT REPORTING SYSTEM (AERS)
OFFICE OF POSTMARKETING DRUG RISK ASSESSMENT
BRIEF DESCRIPTION WITH CAVEATS OF SYSTEM
JUNE 25, 1998

IMPORTANT INFORMATION:

THE ADVERSE EVENT REPORTING SYSTEM (AERS) IN THE OFFICE OF POSTMARKETING DRUG RISK ASSESSMENT (PDRA) HAS BEEN IMPLEMENTED TO TAKE ADVANTAGE OF UP-TO-DATE METHODS FOR DATA ENTRY AND DATABASE DESIGN. AERS WILL CONTAIN ALL REPORTS RECEIVED SINCE NOVEMBER 1, 1997.

BACKGROUND:

THE AERS DATABASE IS A NEWLY COMPUTERIZED SYSTEM FOR STORING ADVERSE EVENTS REPORTED BY HEALTH PROFESSIONALS AND OTHERS. THE SYSTEM CONTAINS ADVERSE EVENTS DETECTED AND REPORTED AFTER MARKETING OF THE DRUG .

AERS DEPENDS ON A HEALTH PROFESSIONAL'S DETECTING A NEW CLINICAL EVENT, ATTRIBUTING THE APPEARANCE OF THE CLINICAL EVENT TO THE ADMINISTRATION OF A DRUG , AND REPORTING THAT CLINICAL EVENT TO A DRUG COMPANY OR THE FDA.

THE HEALTH PROFESSIONAL MAY CHOOSE TO REPORT THE ADVERSE REACTION TO A DRUG FIRM, WHO MUST, BY LAW, REPORT TO THE FDA. NINETY PERCENT OF OUR REPORTS ARE RECEIVED FROM DRUG MANUFACTURERS. OUR OFFICE RECEIVES THE REMAINING TEN PERCENT DIRECTLY FROM OTHER REPORTER(S) (I.E., HEALTH PROFESSIONALS AND CONSUMERS).

DATA FROM ALL REPORTS ARE ENTERED INTO AERS AND THE REPORT IMAGES ARE SCANNED INTO AN ELECTRONIC FILING SYSTEM (EFS) FILING SYSTEM . ALL REPORTS ARE RETRIEVED BY ACCESSING THE "ISR NUMBER".

COPIES OF INDIVIDUAL CASE SAFETY REPORTS WHICH ARE SUMMARIZED IN THIS PRINTOUT MAY BE OBTAINED BY SUBMITTING A SEPARATE FOI REQUEST. WHEN REQUESTS ARE SUBMITTED FOR COPIES OF REPORT IMAGES, THE ISR NUMBER SHOULD BE LISTED IN TABULAR FORMAT IN ASCENDING ORDER AS SHOWN IN THE FOLLOWING EXAMPLE:

ISR NUMBER
3000913-1-00
3000917-9-00
3001581-5-00

THERE IS A $14.00/HOUR SEARCH TIME AND A $.50/PAGE COPY CHARGE. PLEASE NOTE THAT THERE WILL BE REDACTIONS MADE TO ALL IDENTIFIERS ON THE REPORT.

CAVEATS:

THERE ARE IMPORTANT THINGS TO REMEMBER WHEN REVIEWING OR ANALYZING DATA FROM AERS.

1. REPORTS CONTAIN ONLY THOSE REACTIONS VOLUNTARILY SUBMITTED EITHER DIRECTLY TO THE FDA OR TO THE DRUG MANUFACTURER BY CONSUMERS AND/OR MEMBERS OF THE HEALTH PROFESSION AND WHICH HAVE BEEN ENTERED INTO THE AERS COMPUTERIZED FILING SYSTEM SINCE NOVEMBER 1, 1997.

2. THE INFORMATION CONTAINED IN THE REPORTS HAS NOT BEEN SCIENTIFICALLY OR OTHERWISE VERIFIED AS TO A CAUSE AND EFFECT RELATIONSHIP AND CANNOT BE USED TO ESTIMATE THE INCIDENCE OF ADVERSE DRUG REACTIONS.

3. FOR ANY GIVEN REPORT, THERE IS NO CERTAINTY THAT THE SUSPECTED DRUG CAUSED THE REACTION. THIS IS BECAUSE PHYSICIANS ARE ENCOURAGED TO REPORT SUSPECTED REACTIONS. THE EVENT MAY HAVE BEEN RELATED TO THE UNDERLYING DISEASE FOR WHICH THE DRUG WAS GIVEN TO CONCURRENT DRUG BEING TAKEN OR MAY HAVE OCCURRED BY CHANCE AT THE SAME TIME THE SUSPECTED DRUG WAS TAKEN.

4. ACCUMULATED CASE REPORTS CANNOT BE USED TO CALCULATE INCIDENCE OR ESTIMATES OF DRUG RISK.

5. NUMBERS FROM THESE DATA MUST BE CAREFULLY INTERPRETED AS REPORTING RATES AND NOT OCCURRENCE RATES. TRUE INCIDENCE RATES CANNOT BE DETERMINED FROM THIS DATA BASE. COMPARISONS OF DRUGS CANNOT BE MADE FROM THESE DATA.

DEFINITIONS OF THE LINE LISTING OF CASES

YEAR — YEAR THE REPORT WAS RECEIVED.

ISR NUMBER — A UNIQUE NUMBER ASSIGNED SEQUENTIALLY TO A REPORT FOR INTERNAL PROCESS CONTROL AND SCANNING. REPORTS ARE THEN RETRIEVED AND PRINTED FROM THE ELECTRONIC ARCHIVES USING THIS NUMBER.

REPORT TYPE	THE TYPE OF REPORT SUBMITTED: EXPEDITED (15-DAY) FROM THE MANUFACTURER AND DIRECT (VOLUNTARY REPORTING).
COMPANY REPORT #	NUMBER ASSIGNED BY THE MANUFACTURER OF THE DRUG.
AGE	AGE IN YEARS, OR OTHER INDICATED UNITS.
GENDER	MALE FEMALE UNKNOWN NOT SPECIFIED
OUTCOME	THE RESULTS OF THE ADVERSE EVENT AS IDENTIFIED ON THE MEDWATCH REPORTING FORM. THE FOLLOWING EVENTS ARE POTENTIAL CHOICES: DEATH, LIFE-THREATENING, HOSPITALIZATION (INITIAL OR PROLONGED) DISABILITY, CONGENITAL ANOMALY, REQUIRED INTERVENTION TO PREVENT PERMANENT IMPAIRMENT/DAMAGE.

OUTCOME CODE	DESCRIPTION
DE	DEATH
LT	LIFE-THREATENING
HO	HOSPITALIZATION - INITIAL OR PROLONGED
DS	DISABILITY
CA	CONGENITAL ANOMALY
RI	REQUIRED INTERVENTION TO PREVENT PERMANENT IMPAIRMENT/DAMAGE
OT	OTHER

PREFERRED TERM (PT)	THE REPORTED REACTION(S) CODED FROM. THE ICH INTERNATIONAL MEDICAL TERMINOLOGY THESAURUS (MEDDRA).
REPORT SOURCE	THE REPORT SOURCE OF THE ADVERSE EVENT.
PRODUCT	NAME OF DRUG .

ROLE	*S = SUSPECT C=CONCOMITANT PS = PRIMARY SUSPECT SS = SECONDARY SUSPECT
*SUSPECT DRUG(S)	THE DRUG(S) THAT THE INITIAL REPORTER DEEMED MOST LIKELY TO BE ASSOCIATED WITH THE REACTION(S). DRUG(S) ARE CODED AS EITHER ('S') FOR SUSPECT OR ('C') FOR CONCOMITANT.
MANUFACTURER	THE COMPANY THAT MANUFACTURES THE DRUG.
ROUTE	ROUTE OF ADMINISTRATION OF THE DRUG(S) (E.G., IV, PO. TOP, ETC.).
DAILY DOSE	QUANTITY OF DRUG ADMINISTERED IN A 24-HOUR PERIOD.
UNITS	MODIFIES THE DAILY DOSE WITH UNITS OF MEASUREMENT (E.G., MG, IU, ML, ETC.).
DURATION	NUMBER OF DAYS THE DRUG WAS USED.

FDA - Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Summary report for FOI selections:

Selection by inexact search of active ingredient: SALICYLIC_ACID%

Selection by inexact search of Tradename/Verbatim: NOPROD%

Total number of reports: 41

From: 01 NOV 1997 To: Present

19 Jan 2001 01:23 PM

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 11/05/97 ISR Number: 3005373-2 Report Type: Direct Company Report # Age: Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
	Unevaluable Reaction		Clinique	PS	Estee Lauder Inc	TOPICAL	ANTI-ITCH LOTION&CREAM (CONTAIN HYDROCORTISON E ACETATE)

Date: 01/20/98 ISR Number: 3017929-1 Report Type: Expedited (15-Day) Company Report # 199810056HPD Age:11 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Dermatitis Bullous	Foreign	Claforan	PS			1 G BID IVF
Initial or Prolonged	Dermatitis Nos	Study	Streptomycin Sulfate	SS		ORAL	1 TSP BID PO
3 DAY							
	Mucosal Ulceration Nos	Health	Clemizole Pencillin	SS			
3 DAY							
	Stevens Johnson Syndrome	Professional	Streptomycin Pantothenate	SS			
3 DAY							
			Sulfamerazine	SS		ORAL	PO
			Trimethoprim	SS		ORAL	PO
			Acetylsalicylic Acid	SS		ORAL	PO
3 DAY							
			Calcium Carbonate	SS		ORAL	PO
3 DAY							
			Gentamicin	SS		INTRAVENOUS DRIP	
80 MG BID IV							
			Acetylsalicylic Acid	SS		ORAL	500 MG TID PO
			Noscapine Resin	SS		ORAL	TID PO
3 DAY							

			Xylometazoline Hydchloride	SS	PRN
			Silver Diacetyltannin Albuminate	SS	PRN IN
			Ambroxol Hydrochloride	SS	ORAL 1 TSP TID PO
			Tocopheryl Acetate	C	
			Retinol Palmitate	C	

Date: 01/23/98 ISR Number: 3018022-4 Report Type: Expedited (15-Day) Company Report # 199810096HPD Age:82 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration Hospitalization Initial or Prolonged	Blister Mucosal Erosion Nos Rash Erythematous Stevens Johnson Syndrome	Foreign Study Health Professional	Furosemide	PS		ORAL	PO
			Acetylsalicylic Acid	SS		ORAL	100-0-0 MG QAM PO
			Isosorbide Mononitrate	SS		ORAL	20-20-0 MG QD PO
			Potassium Chloride	SS		ORAL	PO
			Bisacodyl	SS		UNKNOWN	ONCE, UNKNOWN
			Lactulose	SS		ORAL	1 TBSP BID PO
			Heparin	SS		SUBCUTANEOUS	7500 IU BID SC
			Pentoxifylline	C			
			Digitoxin	C			

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 01/26/98 ISR Number: 3019538 7 Report Type: Expedited (15-Day) Company Report # 199810105HPD Age:66 YR Gender: Female I/FU: F

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Hospitalization - Initial or Prolonged	Blister	Foreign	Furosemide	PS		INTRAVENOUS DRIP	
ONCE IV 1 DAY	Dermatitis Nos	Study					
	Hypersensitivity Nos	Health	Furosemide	SS		ORAL	PO
	Mouth Ulceration	Professional	Parecetamol	SS		RECTAL	R
	Pain Nos		Diclofenac Sodium	SS			QM
2 DAY	Skin Disorder Nos		Diclofenac	SS		INTRAMUSCULAR	ONCE IM
1 DAY	Skin Ulcer Nos		Diclofenac	SS		INTRAMUSCULAR	ONCE IM
1 DAY	Stevens Johnson Syndrome		Furosemide	SS		ORAL	ONCE PO
1 DAY			Furosemide	SS		ORAL	ONCE PO
1 DAY			Furosemide	SS		INTRAVENOUS DRIP	
ONCE IV 1 DAY			Digoxin	SS		INTRAVENOUS DRIP	
ONCE IV 1 DAY			Digitoxin	SS		INTRAVENOUS DRIP	
IV 2 DAY			Digitoxin	SS		ORAL	PO
			Verapamil Hydrochloride	SS		INTRAVENOUS DRIP	
ONCE IV 1 DAY			Diclofenac Sodium	SS		ORAL	PO
2 DAY			Diclofenac Sodium	SS		RECTAL	R
6 DAY			Isosorbide Mononitrate	SS		ORAL	PO

1	DAY	Isopromethazine	SS	ORAL	ONCE PO
1	DAY	Isopromethazine Hydrochloride	SS	ORAL	ONCE PO
1	DAY	Nifedipine	SS	ORAL	ONCE PO
		Nifedipine	SS	ORAL	QD PO
		Naloxone Hydrochloride	SS	ORAL	PO
		Tilidine Hydrochloride	SS	ORAL	PO
		Streptomycin Sulfate	SS	ORAL	PO
1	WK	Clemizole	SS	ORAL	PO
1	WK	Streptomycin Pantothenate	SS	ORAL	PO
1	WK	Misoprostol	SS	ORAL	PO
		Acetylsalicylic Acid	SS	ORAL	ONCE PO
1	DAY	Codeine Phosphate	SS	ORAL	ONCE PO
1	DAY	Phenacetin	SS	ORAL	ONCE PO
1	DAY	Acetylsalicylic	SS	ORAL	PO
2	DAY	Codeine Phosphate	SS	ORAL	PO
2	DAY	Phenacetin	SS	ORAL	PO
2	DAY	Levomepromazine Maleate	SS	ORAL	ONCE PO
1	DAY	Clorazepate Dipotassium	SS	ORAL	ONCE PO
1	DAY	Zolpidem	SS	ORAL	PO
		Dexamethasone Sodium Phosphate	SS	INTRAMUSCULAR	IM
		Lactulose	SS		
		Dimetindene Maleate	C		
		Clemastine	C		
		Methylprednisolone	C		

FDA - Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 04/25/98 ISR Number: 3132835 X Report Type: Periodic Company Report # 8-98035-016N Age:61 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Dermatitis Nos	Health	Lodine Tablets	PS		ORAL	400 MG
	Eye Pain	Professional	Havrix Injection	SS		INTRAMUSCULAR	
	Pharyngitis Nos		Pain Bust-R Ii (Salicylic Acid And Menthol)	SS		TOPICAL	
	Pruritus		Tetanus Toxoid Injection	SS		INTRAMUSCULAR	
			Typhoid Vaccine Injection	SS		INTRAMUSCULAR	
			Hytrin	C			

Date: 04/15/98 ISR Number: 3063924 6 Report Type: Expedited (15 Day) Company Report # 8 98092 024A Age:76 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Life-Threatening	Drug Interaction Nos	Foreign	Amiodarone	PS		INTRAVENOUS DRIP	
Other	Haematoma Nos	Health					
IV INJ							
	Retroperitoneal Haemorrhage	Professional	Acetylsalicylic Acid	SS		ORAL	125 MG ORAL
			Heparin Sodium	SS		INTRAVENOUS DRIP	
IV							
			Glyceryl Trinitrate	C			
			Nifedipine	C			

Date: 04/23/98 ISR Number: 3072715-1 Report Type: Direct Company Report # Age:48 YR Gender: Female I/FU: I

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Other	Drug Ineffective		Orphen/Asa/Caf* 50/770/60t	PS			1 @ 4 TO 6 HOURS

Date: 05/08/98 ISR Number: 3085278 1 Report Type: Direct Company Report # Age: Gender: I/FU: I

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
	Burns Nos	Consumer	Revco Wart Liquid	PS			
	Skin Infection Nos						

Date: 06/23/98 ISR Number: 3097677-2 Report Type: Expedited (15-Day) Company Report # WAES 98060615 Age:47 YR Gender: Male I/FU: I

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Hospitalization	Anuria	Foreign	Noroxin	PS		ORAL	400 MG
4 DAY							
Initial or Prolonged	Fatigue	Health	Acetaminophen (+)				
	Glycosuria Present	Professional	Salicylamide	SS		ORAL	2 GM
4 DAY							
	Hepatic Disorder Nos		Thiaton	SS		ORAL	30 MG
4 DAY							
	Hepatocellular Damage		Antimicrobial				
	Jaundice Nos		Therapy	SS		ORAL	3 GM
4 DAY							
	Liver Function Tests Nos		Primperan	SS		ORAL	15 MG
4 DAY							
	Abnormal						
	Proteinuria Present						
	Renal Failure Acute						

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 07/09/98 ISR Number: 3103822 2 Report Type: Expedited (15-Day) Company Report # 1998070082 Age:65 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Disability	Blister	Foreign	Diprolene	PS		TOPICAL	TOP DERM
1 DAY							
	Burns First Degree	Health	Salicylic Acid	SS		TOPICAL	TOP DERM
1 DAY							
	Rash Erythematous	Professional	Anaxeryl	SS		TOPICAL	TOP DERM
1 DAY							
	Rash Macular	Other					

Date: 07/30/98 ISR Number: 3111128-0 Report Type: Expedited (15-Day) Company Report # 002-0981-980030(0) Age:36 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Death	Activated Partial	Health	Lipitor	PS		ORAL	10 MG
34 DAY							
Hospitalization	Thromboplastin Time	Professional	Acetylsalicylic Acid	SS		ORAL	325 MG
Initial or Prolonged	Prolonged						(DAILY)
34 DAY							
	Anorexia		Acetaminophen				
	Chromosome Analysis Nos		(Paracetamol)	C			
	Abnormal						
	Coagulation Disorder Nos						
	Depressed Level Of						
	Consciousness						
	Diarrhoea Nos						
	Haemoglobin Decreased						
	Headache Nos						
	International Normalised						
	Ratio Increased						
	Liver Fatty						
	Liver Function Tests Nos						
	Abnormal						
	Myalgia						

Myelodysplastic Syndrome
Nos
Myeloid Metaplasia
Nausea
Pancytopenia
Plasmacytosis
Pyrexia
Renal Impairment Nos
Reye'S Syndrome
Sepsis Nos
Vomiting Nos

Date: 08/07/98 ISR Number: 3114259-4 Report Type: Expedited (15-Day) Company Report # 98-025 Age:72 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Fall	Foreign	Selegiline	PS			10MG/DAY
2213 DAY							
	Gait Abnormal Nos	Health	Pergolide	SS			
		Professional	Levodopa	SS			
		Distributor	Enalapril	SS			
			Furosemide	SS			
			Isosorbide Dinitrate	SS			
			Acetylsalicylic Acid	SS			

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 09/04/98 ISR Number: 3126445-8 Report Type: Expedited (15-Day) Company Report # FR52-00595 Age:84 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Antinuclear Factor	Foreign	Coversyl	PS	Servier	ORAL	2 MG/QD/PO
Initial or Prolonged	Positive		Zopiclone	SS			
	Blood Immunoglobulin G		Acetylsalicylic Acid	SS			
	Increased		Cacit	SS			1000 MG
	Blood Immunoglobulin M						
	Increased						
	Cold Agglutinins Positive						
	Complement Factor Nos						
	Decreased						
	Connective Tissue						
	Disorder Nos						
	Cryoglobulinuria Present						
	Inflammation Nos						
	Oedema Lower Limb						
	Vascular Purpura						

Date: 09/11/98 ISR Number: 3127540-X Report Type: Expedited (15-Day) Company Report # 9826921 Age:86 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Drug Interaction Nos	Foreign	Feldene	PS		ORAL	ORAL
Initial or Prolonged	Haematemesis	Health	Prednisolone	SS		ORAL	ORAL
Required	Haematocrit Decreased	Professional	Acetylsalicylate De				
Intervention to	Haemoglobin Decreased	Other	Lysine	SS		ORAL	ORAL
Prevent Permanent	Hypotension		Allopurinol	C			
Impairment/Damage	Tachycardia Nos		Ofloxacine	C			
			Paracetamol + Dextropropoxyphene	C			
			Trinitrine	C			
			Furosemide	C			
			Acetamin/Cafe/Carbas pc/Chlorph/Dextrop	C			

Date: 09/14/98 ISR Number: 3132442 9 Report Type: Expedited (15-Day) Company Report # 9826921 Age:86 YR Gender: Male I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Drug Interaction Nos	Foreign	Feldene	PS		ORAL	ORAL
Initial or Prolonged	Haematocrit Decreased	Health	Prednisolone	SS		ORAL	ORAL
Required	Haemoglobin Decreased	Professional	Acetylsalicylate De				
Intervention to	Heart Rate Increased	Other	Lysine	SS		ORAL	ORAL
Prevent Permanent	Hypotension		Allupurinol	C			
Impairment/Damage			Ofloxacine	C			
			Paracetamol +				
			Dextropropoxyphene	C			
			Trinitrine	C			
			Furosemide	C			
			Acetamin/Caffe/Carba				
			spc/Chlorph/Dextrop	C			

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 10/26/98 ISR Number: 3146927 2 Report Type: Expedited (15-Day) Company Report # B042000 Age: Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Death	Blood Creatine Increased	Foreign	Captopril	PS		ORAL	50 MG BID
Life Threatening	Dyspnoea Nos	Health					ORAL
Hospitalization	Eosinophilia (Exc	Professional	Hydrochlorothiazide	SS			12.5 MG BID
Initial or Prolonged	Pulmonary)		Acetylsalicylic Acid	SS		ORAL	100 MG QD
	Epistaxis						ORAL
	Haematoma Nos		Metoprolol	SS		ORAL	25 MG BID
	Idiopathic						ORAL
	Thrombocytopenic Purpura		Glyceryl Nitrate	C			
	Ileus						
	Platelet Count Decreased						
	Renal Failure Acute						
	Thrombocytopenia						

Date: 10/29/98 ISR Number: 3151481 5 Report Type: Expedited (15 Day) Company Report # 981021 008014141 Age:82 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Death	Blister	Foreign	Haldol	PS		INTRAVENOUS	
Life Threatening	Diaphragmatic Paralysis	Health				DRIP	
UNKNOWN,							
	Epidermal Necrolysis	Professional					ONCE, IV
	Multi Organ Failure						(INTRAVENOUS)
	Rash Erythematous		Haldol	SS		ORAL	UNKNOWN, QD,
							ORAL
			Oxazepam	SS		ORAL	10 MG, QD,
							ORAL
			Gelonida	SS		ORAL	ORAL
			Furosemide	SS		ORAL	10 MG, QD,
							ORAL; 40
							MG, QD, ORAL
			Furosemide	SS		INTRAVENOUS	
						DRIP	

			IV (INTRAVENOUS)
Gentamicin	SS	ORAL	10 MG, QD, ORAL
Tramadol	SS	ORAL	UNKNOWN, ONCE, ORAL
Diazepam	SS	INTRAVENOUS DRIP	
Lorazepam	SS	INTRAMUSCULAR	IV 2.5 MG, QD, IM (INTRAMUSCULAR)
Heparin Sodium	SS	SUBCUTANEOUS	7500 U, UNKNOWN, SC (SUBCUTANEOUS)
Heparin	SS	INTRAVENOUS DRIP	
			UNKNOWN, IV (INTRAVENOUS)
Lysine Acetylsalicylate	SS	INTRAVENOUS DRIP	
			ONCE, IV (INTRAVENOUS)

[illegible], QD,

10 MG, ONCE,

UNKNOWN,

UNKNOWN,

	Dytide H	SS	ORAL	UNKNOWN, BID, ORAL
	Ampicillin	SS	INTRAVENOUS DRIP	2 G, QD, IV (INTRAVENOUS)
	Glycerol	SS	INTRAVENOUS DRIP	UNKNOWN,
	Mezlocillin	SS	SUBCUTANEOUS	UNKNOWN, IV (INTRAVENOUS)
	Isoket	SS	ORAL	10 U, QD, SC (SUBCUTANEOUS)
	Promethazine	SS	INTRAVENOUS DRIP	40 MG, ONCE, ORAL
	Promethazine	SS	ORAL	UNKNOWN, QD, ORAL
	Acetylsalicylic Acid	SS	ORAL	100 MG, QD, ORAL
	Glimepiride	C		
	Naftidrofuryl	C		
	Spironolactone	C		
	Sodium Chloride	C		
	Normofundin	C		
	Kalinor	C		
	Morphine	C		
	Trifluoperazine	C		
	Dopamine	C		
	Dobutamine	C		
	Tutofusin	C		

Date: [illegible] ISR Number: [illegible] Report Type: Expedited (15 Day) Company Report # 9839167 Age:49 YR Gender: Male I/FU:

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Hepatic Necrosis	Foreign	Norvasc	PS		ORAL	5.00 MG TOTAL:DAILY:ORAL
Initial or Prolonged	Serum Ferritin Increased	Health Professional					
	Transaminase Nos Increased	Other	Acetylsalicylate De Lysine	SS		ORAL	230.00 MG TOTAL:DAILY:ORAL
			Simvastatin	SS		ORAL	DAILY:ORAL

Date: 12/15/98 ISR Number: 3171222-5 Report Type: Expedited (15-Day) Company Report # 422/20287 Age:83 YR Gender: Male I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Life Threatening	Epidermal Necrolysis	Foreign	Fragmin	PS		SUBCUTANEOUS	SC
Hospitalization	Rash Vesicular	Consumer	Tramadol Hcl	SS			
Initial or Prolonged		Company	Lormetazepam	SS			
Other		Representative	Acetylsalicyclic Acid	SS			
			Glibenclamide	SS			
			Codiovan	SS			
			Ciprofloxacin Hcl	SS			

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Nifedipine	SS
Hypericum Extract	SS
Fentanyl	SS
Bactrim	SS
Novalgin	SS
Agiolax	C
Hypericum Extract	C
Normofundin	C
Ginko Tree Leaves	C
Omeprazole	C
Amlodipine Besilate	C
Metamizole Sodium	C
Digoxin Hcl	C
Flavoxate Hcl	C

Date: 01/08/99 ISR Number: 3178111-0 Report Type: Expedited (15-Day) Company Report # 1998-12-0859 Age:37 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Dyspnoea Nos	Foreign	Dr. Scholl'S Soft				
	Hypersensitivity Nos	Other	Corn Removers Disc	PS		TOPICAL	UNKNOWN TOP DERM
	Pruritus						
	Urticaria Nos						

Date: 01/29/99 ISR Number: 3189295-2 Report Type: Expedited (15-Day) Company Report # 1999-01-0770 Age:80 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization - Initial or Prolonged	Cough	Foreign	Imdur Sustained				
	Dyspnoea Nos	Health	Release Tablets	PS		ORAL	60MG DAILY ORAL
	Pneumonia Nos	Professional					
	Po2 Increased	Other	Ciprofloxacin	SS			
			Atenolol	SS			
			Famotidine	SS			

Salicylic Acid	SS
Metformin Hydrochloride	C
Gliclazide	C

Date: 02/26/99 ICR Number: 3208601-6 Report Type: Direct Company Report # Age:51 YR Gender: Male I/FU: I

Outcome Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Hospitalization Initial or Prolonged	Ammonia Increased		Depakote 750mg Tid	PS			750MG TID
	Aphasia		Salicylic Acid/Dalsaiate 750mg	SS			750MG TID
	Convulsions Nos						
	Aggravated						
	Drug Interaction Nos						
	Encephalopathy Nos						
	Hepatotoxicity Nos						
	Platelet Count Decreased						
	Thrombocytopenia						

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 03/24/99 ISR Number: 3225994-1 Report Type: Expedited (15-Day) Company Report # 99-00709 Age:71 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Death	Acute Circulatory Failure	Foreign	Fragmin	PS		SUBCUTANEOUS	7500 IU TWICE DAILY; SUBCUTANEOUS
Life Threatening	Adult Respiratory Distress Syndrome	Study					
Hospitalization		Health					
Initial or Prolonged	Cardiac Arrest	Professional	Acetylsalicylic Acid	SS			
Disability	Cardiac Fibrillation Nos						
	Cardiac Pacemaker Malfunction						
	Cardiac Tamponade						
	Dialysis Nos						
	Haematuria Present						
	Multi-Organ Failure						
	Post Operative Haemorrhage						
	Sepsis Nos						

Date: 03/24/99 ISR Number: 3318451-5 Report Type: Periodic Company Report # AT 99 13 US Age:27 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
	Oedema Nos	Consumer	Aldara Cream, 5% /				
	Pain Nos		Imiquimod	PS		TOPICAL	250 MG/3X/ WEEK/ TOPICAL
			Salicylic Acid	SS			

Date: 04/02/99 ISR Number: 3232127-4 Report Type: Expedited (15-Day) Company Report # 1999 03-1081 Age:6 YR Gender: I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Complications Of Maternal	Foreign	Diprosalic				

Exposure To Therapeutic Drugs Learning Disorder Nos	Health Professional Other	Betamethasone Dipropionate/Salicyl ic Acid "Like " Diprosone Cream"	PS			UNKNOWN TOP-DERM	

Date: 04/07/99 ISR Number: 3234798-5 Report Type: Expedited (15-Day) Company Report # 9909683 Age:67 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Pancytopenia	Foreign	Abbott-Tranxene	PS	Abbott	ORAL	PO
Initial or Prolonged		Health Professional	Acetylsalicylic Acid Ranitidine	SS		ORAL	PO
Other		Other	Hydrochlor	C			
			Furosemide	C			
			Omeprazole	C			
			Ticlopidine Hydrochlo	C			

Date: 04/20/99 ISR Number: 3243277-0 Report Type: Expedited (15-Day) Company Report # L99-DEN-00469-01 Age:48 YR Gender: Male I/FU: I

Outcome	PT	Report Source
Death	Accident Nos	Foreign Study

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration		Literature Health Professional	Product	Role	Manufacturer	Route	Dose
		Other	Cipramil Salicylic Acid	PS SS			

Date: 04/20/99 ISR Number: 3243280-0 Report Type: Expedited (15-Day) Company Report # L99-DEN-00465-01 Age:27 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration Death	Completed Suicide	Foreign Study Literature Health Professional Other	Cipramil Salicylic Acid	PS SS			

Date: 07/16/99 ISR Number: 3305678-1 Report Type: Expedited (15-Day) Company Report # L99-DEN-00469-01 Age:48 YR Gender: Male I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration Death	Accident Nos Completed Suicide Drug Level Nos Above Therapeutic Drug Toxicity Nos	Foreign Study Literature Health Professional Other	Cipramil Salicylic Acid	PS SS			

Date: [illegible] ISR Number: [illegible] Report Type: Expedited (15 Day) Company Report # 1999-07 0330 Age:75 YR Gender: Male I/FU:
1

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Subdural Haematoma	Foreign	Diprosalic (Betamethasone Dipropionate/Salicyl ic Acid) Cream				
Initial or Prolonged		Health					
Other		Professional					
		Other	"Like Diprosone	PS		TOPICAL	1 APPLIC. QD TOP-DERM
			Anafranil	C			
			Tiapridal	C			
			Renitec	C			
			Insuline Rapitard	C			

Date: 08/05/99 ISR Number: 3318021-9 Report Type: Direct Company Report # Age: Gender: I/FU:
1

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Drug Maladministration		Sulfasalazine	PS	Mutual Pharm		
			Salsalate (Salicylsalicylic Acid)	SS	Dura Med		

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 08/12/99 ISR Number: 3324677-7 Report Type: Expedited (15-Day) Company Report # 1999-08-0131 Age:13 YR Gender: Female I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization	Endoscopy Small Intestine	Health	Duofilm Liquid				
Initial or Prolonged	Abnormal	Professional	Topical Solution	PS			TOP-DERM
Other	Haemoptysis	Other					
	Mucous Membrane Disorder Nos						
	Oral Pain						
	Rash Erythematous						
	Vomiting Nos						

Date: 09/07/99 ISR Number: 3341593-5 Report Type: Direct Company Report # Age:3 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
	Application Site Pain		Duofilm	PS			ONCE A DAY
	Application Site Reaction Nos						
	Drug Maladministration						
	Rash Erythematous						
	Skin Injury Nos						

Date: 10/04/99 ISR Number: 3368169-8 Report Type: Periodic Company Report # 19980700009 Age:47 YR Gender: Female I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Face Oedema	Consumer	Plendil Tab	PS		ORAL	5 MG QD PO
	Headache Nos						
	Influenza Like Illness		Posicor	SS			
	Insomnia Nec		Analgesics	SS		ORAL	25 MG QD

Cardizem	C
Estrogen Nos	C
Edecrin	C
Potassium	C

Date: 10/12/99 ISR Number: 3370679-4 Report Type: Expedited (15-Day) Company Report # 1999-10-0054 Age:56 YR Gender: Male I/FU: I

Outcome Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Hospitalization Initial or Prolonged Other	Blister Oedema Lower Limb Pain Nos Rash Erythematous	Foreign Health Professional Other	Diprosone (Betamethasone Dipropionate) Ointment	PS			2 APPL QD TOP-DERM
			Synthol Topicals	SS			2 APPL QD TOP-DERM
			Ketum (Ketoprofen) Ointment	SS		TOPICAL	2 APPL QD TOP-DERM

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 10/25/99 ISR Number: 3381550 6 Report Type: Periodic Company Report # 990507-SK668 Age:49 YR Gender: Female I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Other	Dyspepsia	Consumer	Arthrotec 75	PS		ORAL	1.000 TB BID PO
	Rectal Bleeding	Health Professional	Analgesics	SS		ORAL	UNKNONW PO

Date: 07/17/00 ISR Number: 3531024-4 Report Type: Expedited (15-Day) Company Report # 2000-DE-Y0086 Age:57 YR Gender: Male I/FU: F

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Death	Aortic Atherosclerosis	Foreign	Flomax	PS	Boehringer Ingelheim		
	Cardiac Arrest	Health			Pharmaceuticals Inc	ORAL	SEE B.5/PO
122 DAY							
	Coronary Artery Disease	Professional	Eviprostat	SS		ORAL	3 ANZ/PO
109 DAY							
	Nos						
	Hypertension Nos						
	Loss Of Consciousness Nec						
	Myocardial Ischaemia						

Date: 11/06/00 ISR Number: 3608110 3 Report Type: Expedited (15 Day) Company Report # 2000 09 1855 Age:49 YR Gender: Male I/FU: I

Outcome	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Duration							
Hospitalization - Initial or Prolonged	Application Site Erythema	Consumer	Dr. Scholl'S Clear Away Wart Remover				
Required Intervention to Prevent Permanent Impairment/Damage	Application Site Reaction		Disc	PS		TOPICAL	1 DISC TOP DERM
	Nos						
	Blister		Intron A (Interferon				
	Cellulitis		Alfa 2b Recombinant)	C			
	Ecchymosis		Inderal	C			
	Pyrexia		Naprosyn	C			
	Swelling Nos		Hydrocodone	C			

Tylenol C

Date: 11/20/00 ISR Number: 3615202-1 Report Type: Expedited (15-Day) Company Report # A036799 Age: Gender: Female I/FU: I

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
Hospitalization	Application Site Oedema	Foreign	Feldene	PS	Pfizer Laboratories Div Pfizer Inc	INTRAMUSCULAR	INTRAMUSCULAR
Initial or Prolonged	Blood Thromboplastin Decreased	Health Professional	Synthol	SS		TOPICAL	TOPICAL
	Haematoma Nos		Tamoxifene	C			
			Levothyroxine Sodique	C			
			Diclofenac	C			

Date: 11/28/00 ISR Number: 3619421-X Report Type: Periodic Company Report # US1999578 Age:43 YR Gender: Male I/FU: I

Outcome / Duration	PT	Report Source	Product	Role	Manufacturer	Route	Dose
	Condition Aggravated	Consumer	Metrocream	PS	Galderma Laboratories Lp		
	Conjunctivitis Nec						
	Dermatitis Nos		15% Glycolic Acid Lotion	SS			
	Dry Eye Nec		Salicyclic Acid Facial Wash	SS			
	Dry Skin						

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Date: 12/07/00 ISR Number: 3625154 6 Report Type: Expedited (15-Day) Company Report # A036799 Age:61 YR Gender: Female I/FU: F

Outcome Duration Hospitalization Initial or Prolonged	PT	Report Source	Product	Role	Manufacturer	Route	Dose
	Autoantibody Nos Positive	Foreign	Feldene	PS	Pfizer Laboratories Div Pfizer Inc	INTRAMUSCULAR	DAILY INTRAMUSCULAR
	Coagulation Disorder Nos	Health Professional					
	Fall	Other	Synthol	SS		TOPICAL	TOPICAL
	Haematoma Nos		Diclofenac	SS		ORAL	150.00 MG TOTAL ORAL
	Injection Site Oedema		Levothyroxine	SS		ORAL	100.00 MCG TOTAL DAILY ORAL
	Oedema Nos		Tamoxifene	C			

FDA Adverse Event Reporting System (AERS)

Freedom Of Information (FOI) Report

Summary report for FOI selections:

Selection by inexact search of active ingredient: SALICYLIC_ACID%

Selection by inexact search of Tradename/Verbatim: NOPROD%

Total number of reports: 41

From: 01-NOV-1997 To: Present

COMMENTS FOR OLAY CLEANSERS WITH SALICYLIC ACID

NA HEF Comments for O[illegible]leansers with Salicylic Acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Ctry	MD	Incident	Dur	Amount
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LI0717407		Unknown	Male Adult	13-Jan-97	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	OLS0717665		Unknown	Female Adult	14-Jan-97	SWELLING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIN0718607		Unknown	Female Adult	21-Jan-97	WARM	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEA0719521		Unknown	Female Adult	27-Jan-97	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLO0720240		Unknown	Female Adult	31-Jan-97	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	RIZ0720647		Unknown	Female Adult	03-Feb-97	IRRITATION	US	N	EYE	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EST0721100		Unknown	Female Adult	06-Feb-97	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	LIP0721562		Unknown	Female Adult	10-Feb-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAH0722289		Unknown	Female Adult	14-Feb-97	WELTS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUE0723862	30	Year(s)	Female Adult	26-Feb-97	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0723849		Unknown	Female Adult	26-Feb-97	RASH	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEA0724878		Unknown	Female Adult	06-Mar-97	DRYNESS	US	N	SKIN	3	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SCO0727120		Unknown	Unknown	21-Mar-97	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMA0728450	40	Year(s)	Female Adult	01-Apr-97	ACNE	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0728873		Unknown	Unknown	04-Apr-97	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAG0729303		Unknown	Female Adult	08-Apr-97	STINGING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0729323		Unknown	Female Adult	08-Apr-97	BLEMISHES	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAL0729478		Unknown	Female Adult	09-Apr-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAL0729738		Unknown	Unknown	10-Apr-97	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIN0729828		Unknown	Female Adult	11-Apr-97	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WHI0732219	23	Year(s)	Female Adult	28-Apr-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAN0732913	64	Year(s)	Female Adult	02-May-97	BLISTERS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAG0732889	47	Year(s)	Female Adult	02-May-97	DRYNESS	US	N	SKIN		Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	GOL0732942		Unknown	Female Adult	05-May-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROS0732994		Unknown	Female Adult	05-May-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0733138	14	Year(s)	Female Child	05-May-97	BURNING	US	N	SKIN	10	Minute(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SIL0733164		Unknown	Female Adult	06-May-97	RASH	US	N	SKIN	12	Hour(s)
AGE DEFYING SERIES CLEANSER PACKETTE	TAY0733363	48	Year(s)	Female Adult	06-May-97	SWELLING	US	N	SKIN	24	Hour(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	TAY0733223	48	Year(s)	Female Adult	06-May-97	ACNE	US	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SLA0733224		Unknown	Female Adult	06-May-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0733490	21	Year(s)	Female Adult	07-May-97	ACNE	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WHI0733515	22	Year(s)	Female Adult	07-May-97	BURNING	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	TOL0733963		Unknown	Unknown	13-May-97	RACING/PALPIT	US	N	INHALATION	4	Hour(s)
AGE DEFYING SERIES CLEANSER PACKETTE	UNK0734150		Unknown	Female Adult	13-May-97	BURNING	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	DUR0734104		Unknown	Female Adult	13-May-97	DRYNESS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	HER0734152		Unknown	Female Adult	13-May-97	SWELLING	US	N	SKIN		

AGE DEFYING SERIES CLEANSER PACKETTE	BEA0734312		Unknown	Female Adult	14-May-97	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	HOW0734419		Unknown	Female Adult	16-May-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0734459		Unknown	Female Adult	16-May-97	LUMPS	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	ERH0734848		Unknown	Female Adult	19-May-97	PEELING	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	FUN0734897	49	Year(s)	Female Adult	19-May-97	SWELLING	US	N	SKIN	10	Hour(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	VOL0734764		Unknown	Female Adult	19-May-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AUS0734800	52	Year(s)	Female Adult	19-May-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZIN0734911		Unknown	Female Adult	19-May-97	RASH	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	MIL0735003	49	Year(s)	Female Adult	20-May-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0735071		Unknown	Female Adult	20-May-97	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TRU0735054	23	Year(s)	Female Adult	20-May-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	KOP0735430		Unknown	Female Adult	22-May-97	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAL0735647		Unknown	Unknown	23-May-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEW0735550		Unknown	Unknown	23-May-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEW0735550		Unknown	Unknown	23-May-97	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEL0735782	61	Year(s)	Female Adult	27-May-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUB0735878		Unknown	Unknown	27-May-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEE0735811		Unknown	Female Adult	27-May-97	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OPD0735755		Unknown	Unknown	27-May-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0735821		Unknown	Female Adult	27-May-97	REDNESS	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	RYM0735936		Unknown	Female Adult	28-May-97	SWELLING	US	N	SKIN	10	Year(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COR0735905		Unknown	Female Adult	28-May-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FON0735925		Unknown	Female Adult	28-May-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAX0736052		Unknown	Female Adult	28-May-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0736095		Unknown	Female Adult	29-May-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIT0736100	36	Year(s)	Female Adult	29-May-97	PIMPLES	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	VRO0736269	45	Year(s)	Female Adult	30-May-97	SCRATCH	US	N	INJURY	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	KES0736794		Unknown	Female Adult	03-Jun-97	REDNESS	US	Y	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLA0736706		Unknown	Female Adult	03-Jun-97	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEV0736818		Unknown	Female Adult	03-Jun-97	SCRATCH	US	N	EYE	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEI0736677		Unknown	Female Adult	03-Jun-97	BUMPS	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	DUL0737027	37	Year(s)	Unknown	04-Jun-97	N	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRA0736960	22	Year(s)	Female Adult	04-Jun-97	RAW	US	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEV0737000		Unknown	Female Adult	04-Jun-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0737025	20	Year(s)	Female Adult	04-Jun-97	RASH	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BUR0737201		Unknown	Female Adult	05-Jun-97	HIVES	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAM0737106		Unknown	Female Adult	05-Jun-97	IRRITATION	US	N	EYE		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COG0737261		Unknown	Female Adult	06-Jun-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAJ0737256	42	Year(s)	Female Adult	06-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALL0737520	45	Year(s)	Female Adult	09-Jun-97	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0737395		Unknown	Unknown	09-Jun-97	REDNESS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIN0737372		Unknown	Female Adult	09-Jun-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEE0737574	38	Year(s)	Female Adult	09-Jun-97	BUMPS	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BRO0737593		Unknown	Female Adult	10-Jun-97	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LI0737689		Unknown	Female Adult	10-Jun-97	RASH	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0737587		Unknown	Female Adult	10-Jun-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THO0737765		Unknown	Female Adult	10-Jun-97	BUMPS	US	N	SKIN	4	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	ROU0738136	31	Year(s)	Female Adult	12-Jun-97	ITCHING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SET0738027		Unknown	Female Adult	12-Jun-97	ROUGH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIG0738277		Unknown	Female Adult	13-Jun-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAS0738344	32	Year(s)	Female Adult	16-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COB0738549	40	Year(s)	Female Adult	16-Jun-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MUR0738380		Unknown	Female Adult	16-Jun-97	REDNESS	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0738614	70	Year(s)	Female Adult	17-Jun-97	RAW	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAY0738643		Unknown	Female Adult	17-Jun-97	SWELLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAT0738671		Unknown	Female Adult	17-Jun-97	BLISTERS	US	N	SKIN	1	Year(s)
AGE DEFYING SERIES CLEANSER PACKETTE	ALE0738868		Unknown	Female Child	18-Jun-97	REDNESS	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	LEV0738910	50	Year(s)	Female Adult	18-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEN0738871	66	Year(s)	Female Adult	18-Jun-97	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOF0739065		Unknown	Female Adult	19-Jun-97	WRINKLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	UNK0739078	94	Year(s)	Female Adult	19-Jun-97	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ABE0739443		Unknown	Female Adult	23-Jun-97	REDNESS	US	N	SKIN	7	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LYO0739375		Unknown	Female Adult	23-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0739382		Unknown	Female Adult	23-Jun-97	BURNING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COO0739551		Unknown	Female Adult	24-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIC0739564		Unknown	Female Adult	24-Jun-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOR0739566	41	Year(s)	Female Adult	24-Jun-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIA0739878		Unknown	Unknown	25-Jun-97	RASH	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPI0739811	69	Year(s)	Female Adult	25-Jun-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0740011		Unknown	Female Adult	26-Jun-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUL0740019		Unknown	Female Adult	26-Jun-97	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAT0739943		Unknown	Female Adult	26-Jun-97	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EID0739986		Unknown	Female Adult	26-Jun-97	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0740078		Unknown	Female Adult	26-Jun-97	BUMPS	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLO0740186		Unknown	Female Adult	27-Jun-97	BUMPS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	DE 0740482		Unknown	Female Adult	30-Jun-97	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0740529		Unknown	Female Adult	30-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0740567		Unknown	Female Adult	01-Jul-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAS0740893		Unknown	Unknown	02-Jul-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUP0740894		Unknown	Female Adult	02-Jul-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ADA0740982		Unknown	Female Adult	03-Jul-97	ACNE	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIS0741053		Unknown	Unknown	03-Jul-97	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ILL0741020	55	Year(s)	Female Adult	03-Jul-97	RASH	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	AND0741133		Unknown	Female Adult	07-Jul-97	BLISTERS	US	N	SKIN	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DE 0741405		Unknown	Female Adult	08-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEK0741543	41	Year(s)	Female Adult	08-Jul-97	WELTS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	FAR0741638	44	Year(s)	Female Adult	09-Jul-97	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NAR0741615		Unknown	Female Adult	09-Jul-97	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0741756		Unknown	Female Adult	09-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAL0741809	50	Year(s)	Female Adult	10-Jul-97	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PRI0741843		Unknown	Female Adult	10-Jul-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0742015		Unknown	Female Adult	11-Jul-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRE0742244		Unknown	Female Adult	14-Jul-97	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	REI0742518	54	Year(s)	Female Adult	15-Jul-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0742471	45	Year(s)	Female Adult	15-Jul-97	ACNE	US	N	SKIN	20	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHE0742566		Unknown	Female Adult	15-Jul-97	IRRITATION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAY0742387		Unknown	Female Adult	15-Jul-97	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DE 0742416	46	Year(s)	Female Adult	15-Jul-97	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	GEA0742733		Unknown	Female Adult	16-Jul-97	BURNING	US	Y	EYE		
AGE DEFYING SERIES CLEANSER PACKETTE	GRI0742580		Unknown	Female Adult	16-Jul-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUN0742734		Unknown	Female Adult	16-Jul-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0742649	35	Year(s)	Female Adult	16-Jul-97	BURNING	US	Y	SKIN	6	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BEA0742846		Unknown	Unknown	17-Jul-97	REDNESS	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0742798		Unknown	Female Adult	17-Jul-97	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HER0742978		Unknown	Female Adult	18-Jul-97	FLAKING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAN0742952		Unknown	Unknown	18-Jul-97	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIT0742982	84	Year(s)	Female Adult	18-Jul-97	BLISTERS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAH0743200		Unknown	Female Adult	21-Jul-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRO0743353		Unknown	Unknown	22-Jul-97	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIL0743369		Unknown	Female Adult	22-Jul-97	SWELLING	US	Y	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KNI0743398	73	Year(s)	Female Adult	22-Jul-97	BUMPS	US	N	SKIN	3	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAU0743471		Unknown	Female Adult	22-Jul-97	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VIL0743544		Unknown	Female Adult	23-Jul-97	DRYNESS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0743869		Unknown	Female Adult	24-Jul-97	BUMPS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0744298	22	Year(s)	Female Adult	28-Jul-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEL0744075		Unknown	Female Adult	28-Jul-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEN0744265	70	Year(s)	Female Adult	28-Jul-97	ITCHING	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REN0744309		Unknown	Female Adult	28-Jul-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROG0744147		Unknown	Female Adult	28-Jul-97	BURNING	US	N	EYE INDIRECT		
AGE DEFYING SERIES CLEANSER PACKETTE	CZE0744432		Unknown	Female Adult	29-Jul-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NEW0744536		Unknown	Unknown	29-Jul-97	PEELING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHE0744728		Unknown	Unknown	30-Jul-97	DRYNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0744896	33	Year(s)	Female Adult	31-Jul-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LER0744892		Unknown	Unknown	31-Jul-97	RASH	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	LLO0745201		Unknown	Female Adult	04-Aug-97	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EVA0745333	74	Year(s)	Female Adult	04-Aug-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOR0745299	53	Year(s)	Female Adult	04-Aug-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0745406		Unknown	Female Adult	05-Aug-97	RASH	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AND0745700		Unknown	Female Adult	06-Aug-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOB0745783		Unknown	Female Adult	07-Aug-97	ACNE	US	N	SKIN	12	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0746016	67	Year(s)	Female Adult	08-Aug-97	N	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIN0745969		Unknown	Female Adult	08-Aug-97	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0745985		Unknown	Female Adult	08-Aug-97	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	GWY0746338		Unknown	Female Adult	11-Aug-97	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOS0746165		Unknown	Female Adult	11-Aug-97	RASH	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BAY0746412		Unknown	Female Adult	12-Aug-97	BLISTERS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOW0746416		Unknown	Female Adult	12-Aug-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOH0746368	44	Year(s)	Female Adult	12-Aug-97	BUMPS	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAN0746837		Unknown	Female Adult	14-Aug-97	DRYNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCC0746863		Unknown	Female Adult	14-Aug-97	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZIM0746825	65	Year(s)	Female Adult	14-Aug-97	ACNE	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOW0747287	68	Year(s)	Female Adult	18-Aug-97	SORENESS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	ZOE0747724	69	Year(s)	Female Adult	20-Aug-97	SWELLING	US	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0747853		Unknown	Female Adult	20-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAU0747676	50	Year(s)	Female Adult	20-Aug-97	TEARING	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIE0748012		Unknown	Female Adult	21-Aug-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEA0747908		Unknown	Female Adult	21-Aug-97	DRYNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0748139		Unknown	Female Adult	22-Aug-97	BUMPS	US	N	SKIN		Unknown

OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	CUT0748387		Unknown	Female Adult	25-Aug-97	PIMPLES	US	N	SKIN	3	Month(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	MC 0748448		Unknown	Unknown	25-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BEA0748589	27	Year(s)	Female Adult	25-Aug-97	BURNING	US	N	SKIN	5	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEL0748441		Unknown	Female Adult	25-Aug-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRE0748397		Unknown	Female Adult	25-Aug-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0748271		Unknown	Female Adult	25-Aug-97	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEA0748313		Unknown	Female Adult	25-Aug-97	BUMPS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAM0748736		Unknown	Unknown	26-Aug-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROW0748697	42	Year(s)	Female Adult	26-Aug-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AUM0748930		Unknown	Female Adult	27-Aug-97	REDNESS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROS0748911	36	Year(s)	Female Adult	27-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZOM0748869		Unknown	Female Adult	27-Aug-97	N	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DON0749086		Unknown	Female Adult	28-Aug-97	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	GRI0749323		Unknown	Female Adult	29-Aug-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0749274		Unknown	Female Adult	29-Aug-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STE0749246		Unknown	Unknown	29-Aug-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ARF0749470	71	Year(s)	Female Adult	02-Sep-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0749487		Unknown	Female Adult	02-Sep-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIC0749950	29	Year(s)	Female Adult	04-Sep-97	PIMPLES	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIN0750013	39	Year(s)	Female Adult	04-Sep-97	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0749899	47	Year(s)	Female Adult	04-Sep-97	ITCHING	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	GIL0750224		Unknown	Unknown	05-Sep-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOW0750154		Unknown	Female Adult	05-Sep-97	DRYNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0750097		Unknown	Female Adult	05-Sep-97	BURNING	US	N	SKIN	4	Hour(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	HUS0750483	46	Year(s)	Female Adult	08-Sep-97	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAW0750350		Unknown	Female Adult	08-Sep-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0750363		Unknown	Female Adult	08-Sep-97	DRYNESS	US	N	SKIN	6	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	STO0750969	69	Year(s)	Female Adult	10-Sep-97	REDNESS	US	N	SKIN	30	Minute(s)
OLAY AGE DEFYING RENEWAL CLEANSER	SCH0750874		Unknown	Unknown	10-Sep-97	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0751039	55	Year(s)	Female Adult	11-Sep-97	ITCHING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COX0751056		Unknown	Female Adult	11-Sep-97	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0751097		Unknown	Unknown	11-Sep-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0751076		Unknown	Female Adult	11-Sep-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUL0751377	39	Year(s)	Female Adult	12-Sep-97	PIMPLES	US	N	SKIN	5	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	COE0751431		Unknown	Female Adult	15-Sep-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEN0751508		Unknown	Female Adult	15-Sep-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0751611		Unknown	Female Adult	15-Sep-97	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAC0751823		Unknown	Female Adult	16-Sep-97	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAT0751849	35	Year(s)	Female Adult	16-Sep-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAN0751892		Unknown	Female Adult	16-Sep-97	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TRI0751972		Unknown	Female Adult	16-Sep-97	IRRITATION	US	N	EYE INDIRECT	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOU0752162	53	Year(s)	Female Adult	17-Sep-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAG0752013	55	Year(s)	Female Adult	17-Sep-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHE0752205	80	Year(s)	Female Adult	18-Sep-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0752222		Unknown	Female Adult	18-Sep-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0752520		Unknown	Female Adult	19-Sep-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAU0752763	29	Year(s)	Female Adult	22-Sep-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	INT0752964		Unknown	Female Adult	22-Sep-97	PEELING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0752880	60	Year(s)	Female Adult	22-Sep-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEC0752761		Unknown	Female Adult	22-Sep-97	BURNING	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCA0752862		Unknown	Female Adult	22-Sep-97	RASH	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	N0753026		Unknown	Female Adult	23-Sep-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAT0752994		Unknown	Unknown	23-Sep-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAN0753120	21	Year(s)	Female Adult	23-Sep-97	SWELLING	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	WIL0753251	27	Year(s)	Female Adult	24-Sep-97	IRRITATION	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COO0753195	68	Year(s)	Female Adult	24-Sep-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAL0753303		Unknown	Female Adult	24-Sep-97	ACNE	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RYD0753574	55	Year(s)	Female Adult	25-Sep-97	PIMPLES	US	N	SKIN	3	Week(s)
OLAY FCL REG 6.78 OZ	BUR0753513	15	Year(s)	Female Child	25-Sep-97	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ABB0754067	51	Year(s)	Female Adult	29-Sep-97	WARM	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIR0754027		Unknown	Female Adult	29-Sep-97	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIN0754078	53	Year(s)	Female Adult	29-Sep-97	IRRITATION	US	N	EYE INDIRECT	1	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	BRY0754222		Unknown	Female Adult	30-Sep-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOR0754148		Unknown	Female Adult	30-Sep-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ELL0754449		Unknown	Female Adult	01-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEN0754442		Unknown	Female Adult	01-Oct-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOM0754657		Unknown	Female Adult	02-Oct-97	PIMPLES	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KON0754557		Unknown	Female Adult	02-Oct-97	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAC0754708	70	Year(s)	Female Adult	02-Oct-97	N	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GEN0754905		Unknown	Unknown	03-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAS0755068		Unknown	Female Adult	06-Oct-97	SCRATCH	US	N	INJURY	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	n		Unknown	Female Adult	06-Oct-97	SCRATCH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUS0755195		Unknown	Female Adult	06-Oct-97	SCRATCH	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	FOR0755440		Unknown	Female Adult	07-Oct-97	REDNESS	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEI0755380	20	006	Female Child	07-Oct-97	OTHER	US	N	INGESTION	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MEL0755462	26	Year(s)	Female Adult	07-Oct-97	PIMPLES	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	HOU0755764		Unknown	Female Adult	08-Oct-97	BURNING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRI0755600		Unknown	Female Adult	08-Oct-97	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LUE0755757		Unknown	Female Adult	08-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAM0755950		Unknown	Unknown	09-Oct-97	BLEMISHES	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EDG0756202		Unknown	Female Adult	10-Oct-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LON0756204		Unknown	Unknown	10-Oct-97	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOP0756123		Unknown	Female Adult	10-Oct-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAT0756090		Unknown	Female Adult	10-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAG0756313		Unknown	Female Adult	13-Oct-97	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAN0756291		Unknown	Female Adult	13-Oct-97	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OUZ0756736	36	Year(s)	Female Adult	14-Oct-97	IRRITATION	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUB0756651	60	Year(s)	Female Adult	14-Oct-97	SWELLING	US	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRI0756963		Unknown	Female Adult	15-Oct-97	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAI0756917		Unknown	Female Adult	15-Oct-97	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEE0757068	26	Year(s)	Female Adult	16-Oct-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WUU0757070	45	Year(s)	Female Adult	16-Oct-97	REDNESS	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	MIN0757306		Unknown	Female Adult	17-Oct-97	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COD0757294		Unknown	Unknown	17-Oct-97	WELTS	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	HEN0757583		Unknown	Female Adult	20-Oct-97	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0757772	27	Year(s)	Female Adult	20-Oct-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAN0757804	44	Year(s)	Female Adult	20-Oct-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KUG0757536		Unknown	Female Adult	20-Oct-97	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHI0757757		Unknown	Female Adult	20-Oct-97	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WHI0757801	42	Year(s)	Female Adult	20-Oct-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOO0757708		Unknown	Female Adult	20-Oct-97	ACNE	US	N	SKIN	5	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	POW0757862		Unknown	Female Adult	21-Oct-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EIS0758133		Unknown	Female Adult	22-Oct-97	ACNE	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOL0758339		Unknown	Female Adult	23-Oct-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAL0758362	56	Year(s)	Female Adult	23-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0758294		Unknown	Female Adult	23-Oct-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SOL0758297	70	Year(s)	Female Adult	23-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STR0758421		Unknown	Female Adult	23-Oct-97	RASH	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WRI0758613		Unknown	Female Adult	24-Oct-97	N	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YOU0758537	62	Year(s)	Female Adult	24-Oct-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIE0758894		Unknown	Female Adult	27-Oct-97	STINGING	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOC0758792		Unknown	Female Adult	27-Oct-97	BURNING	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0758967		Unknown	Female Adult	27-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIT0758928	58	Year(s)	Female Adult	27-Oct-97	IRRITATION	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HER0758691		Unknown	Female Adult	27-Oct-97	SWELLING	US	N	SKIN		
OLAY FFW LOT SEN 6.78 OZ	MON0758920		Unknown	Female Adult	27-Oct-97	STINGING	US	N	EYE INDIRECT		
AGE DEFYING SERIES CLEANSER PACKETTE	COL0759118		Unknown	Female Adult	28-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TOD0759437		Unknown	Female Adult	29-Oct-97	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAR0759704	41	Year(s)	Female Adult	30-Oct-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAS0759958		Unknown	Female Adult	03-Nov-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEN0760223	33	Year(s)	Female Adult	03-Nov-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOO0760408	46	Year(s)	Female Adult	04-Nov-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZOE0760837		Unknown	Female Adult	06-Nov-97	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOM0761193	40	Year(s)	Female Adult	07-Nov-97	BURNING	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAS0761045	35	Year(s)	Female Adult	07-Nov-97	PEELING	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	CUR0761340		Unknown	Female Adult	10-Nov-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FEL0761286	43	Year(s)	Female Adult	10-Nov-97	WELTS	US	Y	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0761583	45	Year(s)	Female Adult	10-Nov-97	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0761331		Unknown	Female Adult	10-Nov-97	BURNING	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEN0761645		Unknown	Female Adult	11-Nov-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAP0761641		Unknown	Female Adult	11-Nov-97	BURNING	US	N	SKIN		Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FEL0762080	35	Year(s)	Female Adult	12-Nov-97	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0761909		Unknown	Female Adult	12-Nov-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEV0761964	58	Year(s)	Female Adult	12-Nov-97	SWELLING	US	N	SKIN	6	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAN0762225		Unknown	Female Adult	13-Nov-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COR0762321		Unknown	Unknown	14-Nov-97	BUMPS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAS0762433	38	Year(s)	Female Adult	14-Nov-97	INFLAMED	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOR0762382		Unknown	Female Adult	14-Nov-97	PIMPLES	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIC0762565		Unknown	Female Adult	17-Nov-97	SORES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COO0762662		Unknown	Female Adult	17-Nov-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUS0762553	46	Year(s)	Female Adult	17-Nov-97	ACNE	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAN0762546		Unknown	Female Adult	17-Nov-97	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAT0762889		Unknown	Female Adult	18-Nov-97	DRYNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAV0763190		Unknown	Female Adult	19-Nov-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAM0763273	35	Year(s)	Female Adult	19-Nov-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAN0763452	49	Year(s)	Female Adult	20-Nov-97	BURNING	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRU0763511		Unknown	Unknown	20-Nov-97	IRRITATION	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EGE0763596	28	Year(s)	Female Adult	20-Nov-97	ITCHING	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HYN0763520		Unknown	Female Adult	20-Nov-97	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	QUI0763577	76	Year(s)	Female Adult	20-Nov-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIO0763497		Unknown	Female Adult	20-Nov-97	RASH	US	Y	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIN0763702		Unknown	Female Adult	21-Nov-97	BUMPS	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	FRA0763940		Unknown	Female Adult	24-Nov-97	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DES0764394		Unknown	Female Adult	25-Nov-97	ACNE	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MON0764287		Unknown	Female Adult	25-Nov-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIS0764544	34	Year(s)	Female Adult	25-Nov-97	REDNESS	CA	N	SKIN	10	Minute(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SMA0764632	47	Year(s)	Female Adult	26-Nov-97	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOL0764953		Unknown	Female Adult	01-Dec-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0764809		Unknown	Female Adult	01-Dec-97	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAL0765160	67	Year(s)	Female Adult	01-Dec-97	ITCHING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0765207		Unknown	Female Adult	02-Dec-97	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUI0765255		Unknown	Female Adult	02-Dec-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FRE0765498		Unknown	Female Adult	03-Dec-97	PIMPLES	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEL0765713		Unknown	Female Adult	04-Dec-97	DRYNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0765661		Unknown	Female Adult	04-Dec-97	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRE0766012	37	Year(s)	Female Adult	05-Dec-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0766229	25	Year(s)	Female Adult	08-Dec-97	RASH	US	N	SKIN	40	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SHA0766433		Unknown	Female Adult	09-Dec-97	DRYNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OSM0766457		Unknown	Unknown	09-Dec-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SUB0766481		Unknown	Female Adult	09-Dec-97	PEELING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ABE0766861		Unknown	Female Adult	10-Dec-97	RASH	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEI0766659		Unknown	Female Adult	10-Dec-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0766869		Unknown	Female Adult	11-Dec-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEP0766876	74	Year(s)	Female Adult	11-Dec-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ORO0767024	39	Year(s)	Female Adult	11-Dec-97	BLISTERS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0767438	90	Year(s)	Female Adult	15-Dec-97	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0767633	37	Year(s)	Female Adult	16-Dec-97	IRRITATION	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0767816	34	Year(s)	Female Adult	16-Dec-97	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OWE0767806		Unknown	Female Adult	16-Dec-97	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0767758		Unknown	Female Adult	16-Dec-97	PEELING	US	N	SKIN	6	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIT0767877	57	Year(s)	Female Adult	17-Dec-97	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0768673	31	Year(s)	Female Adult	22-Dec-97	BUMPS	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	KNO0768783	46	Year(s)	Female Adult	23-Dec-97	RASH	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0768754		Unknown	Female Adult	23-Dec-97	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	BIL0769211	81	Year(s)	Female Adult	29-Dec-97	DRYNESS	US	N	SKIN	3	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOS0769078		Unknown	Female Adult	29-Dec-97	DIZZINESS	US	Y	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAU0769006	60	Year(s)	Female Adult	29-Dec-97	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0769080		Unknown	Female Adult	29-Dec-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLO0769566		Unknown	Female Adult	31-Dec-97	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SKI0769736		Unknown	Female Adult	31-Dec-97	BURNING	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0769672		Unknown	Female Adult	31-Dec-97	VISION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DYE0769866		Unknown	Unknown	02-Jan-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLO0769975		Unknown	Unknown	02-Jan-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FOS0770010		Unknown	Female Adult	02-Jan-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEV0769859	70	Year(s)	Unknown	02-Jan-98	OTHER	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAL0769854	40	Year(s)	Female Adult	02-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAL0770069		Unknown	Female Adult	05-Jan-98	INFLAMED	US	N	EYE INDIRECT	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KER0770346	38	Year(s)	Female Adult	05-Jan-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIN0770160	35	Year(s)	Female Adult	05-Jan-98	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	UTT0770230		Unknown	Female Adult	05-Jan-98	REDNESS	US	N	SKIN	8	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLO0770476	53	Year(s)	Female Adult	06-Jan-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEN0770528	30	Year(s)	Female Adult	06-Jan-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIE0770449		Unknown	Unknown	06-Jan-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0770375		Unknown	Female Adult	06-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VLA0770402	27	Year(s)	Female Adult	06-Jan-98	ITCHING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRA0770793		Unknown	Female Adult	07-Jan-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POF0770869	31	Year(s)	Female Adult	07-Jan-98	BUMPS	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0771070		Unknown	Female Adult	08-Jan-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0770983		Unknown	Female Adult	08-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ITT0771249		Unknown	Female Adult	09-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POS0771323		Unknown	Female Adult	09-Jan-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0771576	77	Year(s)	Female Adult	12-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEA0771438		Unknown	Female Adult	12-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0771425	66	Year(s)	Female Adult	12-Jan-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TUT0771588	78	Year(s)	Female Adult	12-Jan-98	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAS0771809		Unknown	Male Adult	13-Jan-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DYS0771932	75	Year(s)	Female Adult	14-Jan-98	PIMPLES	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POW0772105	65	Year(s)	Female Adult	14-Jan-98	RAW	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAT0772319		Unknown	Female Adult	15-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	APA0772495	67	Year(s)	Female Adult	16-Jan-98	SWELLING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COX0772378		Unknown	Female Adult	16-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TOD0772472	45	Year(s)	Female Adult	16-Jan-98	BUMPS	US	N	SKIN	24	Hour(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIC0772687	60	Year(s)	Female Adult	20-Jan-98	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUS0772740		Unknown	Female Adult	20-Jan-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DZI0773054		Unknown	Female Adult	21-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIC0773243	63	Year(s)	Female Adult	21-Jan-98	BLEMISHES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COB0773311	40	Year(s)	Female Adult	22-Jan-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POW0773377		Unknown	Female Adult	22-Jan-98	WELTS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHI0773742		Unknown	Female Adult	26-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAY0773864	21	Year(s)	Female Adult	26-Jan-98	ITCHING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AND0774125		Unknown	Female Adult	27-Jan-98	RASH	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAI0774115		Unknown	Female Adult	27-Jan-98	BURNING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0774173		Unknown	Female Adult	27-Jan-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAO0774287		Unknown	Female Adult	27-Jan-98	ACNE	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEI0774625	44	Year(s)	Female Adult	28-Jan-98	DRYNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	D A0774661	40	Year(s)	Female Adult	29-Jan-98	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0774745	35	Year(s)	Female Adult	29-Jan-98	DRYNESS	US	N	SKIN	5	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	LAN0775157		Unknown	Female Adult	02-Feb-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ART0775114		Unknown	Female Adult	02-Feb-98	CHAPPED	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHO0775156		Unknown	Female Adult	02-Feb-98	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEN0775659		Unknown	Female Adult	03-Feb-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAY0775649	32	Year(s)	Female Adult	03-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAI0775523		Unknown	Female Adult	03-Feb-98	REDNESS	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	O^C0775570		Unknown	Female Adult	03-Feb-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOO0775471		Unknown	Female Adult	03-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0775738		Unknown	Female Adult	04-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OVE0775725		Unknown	Female Adult	04-Feb-98	BURNING	US	Y	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAR0775772		Unknown	Female Adult	04-Feb-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOY0775990		Unknown	Unknown	05-Feb-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JAQ0775977		Unknown	Unknown	05-Feb-98	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	YOU0776390		Unknown	Female Adult	09-Feb-98	PIMPLES	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIS0776441		Unknown	Female Adult	09-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0776470		Unknown	Female Adult	09-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0776345		Unknown	Female Adult	09-Feb-98	RASH	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCN0776392		Unknown	Female Adult	09-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAS0776445		Unknown	Female Adult	09-Feb-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEI0776513		Unknown	Female Adult	09-Feb-98	REDNESS	US	N	SKIN	30	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIA0776755		Unknown	Female Adult	10-Feb-98	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROZ0776945		Unknown	Unknown	11-Feb-98	RASH	CA	N	SKIN		

AGE DEFYING SERIES CLEANSER PACKETTE	RIC0777165		Unknown	Female Adult	12-Feb-98	IRRITATION	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	FYF0777195		Unknown	Female Adult	12-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOU0777279		Year(s)	Female Adult	12-Feb-98	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEE0777164		Unknown	Female Adult	12-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEN0777313	52	Year(s)	Female Adult	12-Feb-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ABI0777443		Unknown	Unknown	13-Feb-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0777461	35	Year(s)	Female Adult	13-Feb-98	RASH	US	N	SKIN	1.5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLO0777586	45	Year(s)	Female Adult	16-Feb-98	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0777688		Unknown	Female Adult	17-Feb-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FON0777905		Unknown	Unknown	17-Feb-98	IRRITATION	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEE0777901		Unknown	Unknown	17-Feb-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAL0777859		Unknown	Female Adult	17-Feb-98	RASH	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROG0777960		Unknown	Female Adult	18-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0778154		Unknown	Female Adult	18-Feb-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0778318		Unknown	Female Adult	19-Feb-98	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAB0778251	40	Year(s)	Female Adult	19-Feb-98	RASH	US	N	SKIN	10	Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VIC0778362		Unknown	Female Adult	19-Feb-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLE0778582		Unknown	Female Adult	20-Feb-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOS0778556		Unknown	Female Adult	20-Feb-98	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	KIN0778800		Unknown	Female Adult	23-Feb-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CUM0778908	29	Year(s)	Female Adult	23-Feb-98	RASH	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAN0778656	56	Year(s)	Female Adult	23-Feb-98	RASH	CA	N	SKIN	12	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAV0778991	45	Year(s)	Female Adult	24-Feb-98	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0779332	37	Year(s)	Female Adult	25-Feb-98	SWELLING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0779267		Unknown	Female Adult	25-Feb-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SOM0779328		Unknown	Female Adult	25-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAL0779576		Unknown	Female Adult	26-Feb-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAS0779707		Unknown	Female Adult	27-Feb-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GON0779853		Unknown	Female Adult	27-Feb-98	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRI0780038		Unknown	Female Adult	02-Mar-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAN0780204	43	Year(s)	Female Adult	02-Mar-98	PIMPLES	US	N	SKIN	4	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	MIN0780443	50	Year(s)	Female Adult	03-Mar-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AUG0780288		Unknown	Female Adult	03-Mar-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VAI0780408	42	Year(s)	Female Adult	03-Mar-98	RASH	CA	N	SKIN	4	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEG0780326		Unknown	Female Adult	03-Mar-98	BUMPS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHE0780555	75	Year(s)	Female Adult	04-Mar-98	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHU0780643		Unknown	Female Adult	04-Mar-98	RASH	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KLA0780810		Unknown	Female Adult	05-Mar-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NEL0780981	70	Year(s)	Female Adult	05-Mar-98	SCRATCH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SWI0781235		Unknown	Unknown	06-Mar-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0781287		Unknown	Female Adult	09-Mar-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0781470	21	Unknown	Female Adult	09-Mar-98	DRYNESS	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	RIC0781632		Unknown	Unknown	10-Mar-98	IRRITATION	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	SOR0781683		Unknown	Female Adult	10-Mar-98	BURNING	US	N	SKIN	15	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0781769		Unknown	Female Adult	10-Mar-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MED0781611	30	Year(s)	Female Adult	10-Mar-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TIL0781766	48	Year(s)	Female Adult	10-Mar-98	RASH	CA	N	EYE INDIRECT	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TUR0781684	63	Year(s)	Female Adult	10-Mar-98	WELTS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALV0782067		Unknown	Female Adult	11-Mar-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAA0781953		Unknown	Female Adult	11-Mar-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIL0782084		Unknown	Female Adult	11-Mar-98	BUMPS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COO0782253		Unknown	Female Adult	12-Mar-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEC0782361	47	Year(s)	Female Adult	12-Mar-98	BURNING	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JAH0782151		Unknown	Male Adult	12-Mar-98	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIL0782160		Unknown	Unknown	12-Mar-98	WELTS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIN0782348		Unknown	Female Adult	12-Mar-98	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAK0782494		Unknown	Female Adult	13-Mar-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0782573		Unknown	Female Adult	13-Mar-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EVA0782472		Unknown	Female Adult	13-Mar-98	DRYNESS	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOS0782564		Unknown	Female Adult	13-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAV0782966	56	Year(s)	Female Adult	16-Mar-98	IRRITATION	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAU0782685		Unknown	Female Adult	16-Mar-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOW0782957		Unknown	Female Adult	16-Mar-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEB0783123		Unknown	Female Adult	17-Mar-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAA0783230		Unknown	Female Adult	17-Mar-98	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOR0783155		Unknown	Female Adult	17-Mar-98	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	PAR0783486		Unknown	Female Adult	18-Mar-98	ITCHING	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOG0783498	35	Year(s)	Female Adult	18-Mar-98	REDNESS	CA	Y	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0783348		Unknown	Female Adult	18-Mar-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIN0783438		Unknown	Female Adult	18-Mar-98	RASH	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	DAV0783640		Unknown	Female Adult	19-Mar-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOS0783894	24	Year(s)	Female Adult	20-Mar-98	IRRITATION	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BRE0784142		Unknown	Female Adult	23-Mar-98	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	STR0784197	49	Year(s)	Female Adult	23-Mar-98	ACNE	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAT0784201		Unknown	Female Adult	23-Mar-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LON0784409		Year(s)	Female Adult	23-Mar-98	SWELLING	CA	N	SKIN	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SWA0784405		Unknown	Unknown	23-Mar-98	CHAPPED	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAN0784412		Year(s)	Female Adult	23-Mar-98	SWELLING	CA	N	SKIN	20	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YU0784400		Unknown	Unknown	23-Mar-98	DRYNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0784551	38	Unknown	Female Adult	24-Mar-98	BURNING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEW0784613		Unknown	Unknown	24-Mar-98	SWELLING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0784572		Unknown	Female Adult	24-Mar-98	SWELLING	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OSB0784493		Unknown	Female Adult	24-Mar-98	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0784590		Unknown	Female Adult	24-Mar-98	REDNESS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	USH0784758		Unknown	Female Adult	25-Mar-98	REDNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0785081		Unknown	Unknown	26-Mar-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEG0784913	38	Year(s)	Female Adult	26-Mar-98	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FRA0785173		Unknown	Unknown	27-Mar-98	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THO0785167		Unknown	Female Adult	27-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAL0785421		Unknown	Female Adult	30-Mar-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SUN0785541		Unknown	Female Adult	30-Mar-98	ROUGH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAY0785579		Unknown	Unknown	30-Mar-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ELL0785808		Unknown	Female Adult	31-Mar-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JER0785673		Unknown	Female Adult	31-Mar-98	ROUGH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAN0786066	36	Year(s)	Female Adult	01-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIL0786086		Unknown	Female Adult	01-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TUR0785965	39	Year(s)	Female Adult	01-Apr-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAN0786154		Unknown	Female Adult	02-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PLA0786197	59	Year(s)	Female Adult	02-Apr-98	FLAKING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SER0786162		Unknown	Female Adult	02-Apr-98	WELTS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAN0786420		Unknown	Unknown	03-Apr-98	BURNING	CA	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0786372		Unknown	Female Adult	03-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0786744		Unknown	Female Adult	06-Apr-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUN0786636		Unknown	Female Adult	06-Apr-98	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAI0787127		Unknown	Female Adult	07-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUG0786996		Unknown	Female Adult	07-Apr-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAC0787018		Unknown	Unknown	07-Apr-98	BUMPS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0786936		Unknown	Unknown	07-Apr-98	SCRATCH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIN0786938	48	Year(s)	Female Adult	07-Apr-98	BURNING	US	N	SKIN	10	Minute(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SAL0787139	28	Year(s)	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KLI0787250	38	Year(s)	Female Adult	08-Apr-98	BUMPS	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0787182	56	Year(s)	Female Adult	08-Apr-98	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	OLA0787872	29	Year(s)	Female Adult	13-Apr-98	RASH	US	N	SKIN	18	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ADA0787771	69	Year(s)	Female Adult	13-Apr-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COE0787698	29	Year(s)	Female Adult	13-Apr-98	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIA0787645		Unknown	Female Adult	13-Apr-98	DRY MOUTH	US	N	INHALATION	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZIT0787669		Unknown	Unknown	13-Apr-98	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	BEN0788127		Unknown	Female Adult	14-Apr-98	BUMPS	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FOR0788141	53	Year(s)	Female Adult	14-Apr-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOC0788104		Unknown	Female Adult	14-Apr-98	DRYNESS	US	N	SKIN		
OLAY FACIAL CLEANSING LOTION SIZE ND	LEE0788323		Unknown	Female Adult	15-Apr-98	BUMPS	US	N	SKIN	8	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0788703	37	Year(s)	Female Adult	16-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEL0788606	47	Year(s)	Female Adult	16-Apr-98	RAW	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STR0788570	69	Unknown	Female Adult	16-Apr-98	RASH	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	OTT0788835		Unknown	Female Adult	17-Apr-98	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRA0788747	20	Year(s)	Female Adult	17-Apr-98	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEW0788938	50	Year(s)	Female Adult	17-Apr-98	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MON0789189	24	Year(s)	Female Adult	20-Apr-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SUT0789098	46	Year(s)	Female Adult	20-Apr-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUR0789345	49	Year(s)	Female Adult	21-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAM0789430		Unknown	Unknown	21-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0789763	34	Year(s)	Female Adult	22-Apr-98	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIA0789656		Unknown	Female Adult	22-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIN0789579		Unknown	Female Adult	22-Apr-98	IRRITATION	US	N	SKIN	3	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BAC0789876	75	Year(s)	Female Adult	23-Apr-98	SWELLING	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	JAN0790026		Unknown	Female Adult	23-Apr-98	BURNING	US	N	SKIN		Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EGA0790110	47	Year(s)	Female Adult	24-Apr-98	SWELLING	CA	N	EYE	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DYS0790336		Unknown	Female Adult	27-Apr-98	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MER0790490	62	Year(s)	Female Adult	27-Apr-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STC0790518		Unknown	Female Adult	27-Apr-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAM0790485		Unknown	Female Adult	27-Apr-98	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	BRI0790671		Unknown	Female Adult	28-Apr-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	IZA0790644	30	Year(s)	Female Adult	28-Apr-98	DRYNESS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SER0790854	42	Year(s)	Female Adult	28-Apr-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	LAG0791041		Unknown	Female Adult	29-Apr-98	NG	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AKI0790913	39	Year(s)	Female Adult	29-Apr-98	ACNE	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	D^ 0791127	38	Year(s)	Female Adult	29-Apr-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOM0790939		Unknown	Female Adult	29-Apr-98	RASH	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PHI0791052		Unknown	Female Adult	29-Apr-98	OTHER	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOR0791215	32	Unknown	Female Adult	30-Apr-98	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEN0791172		Unknown	Female Adult	30-Apr-98	SORENESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0791520		Unknown	Female Adult	01-May-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VOR0791573		Unknown	Female Adult	01-May-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HYB0791657		Unknown	Female Adult	04-May-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POO0791880	40	Year(s)	Female Adult	04-May-98	N	US	N	SKIN	4	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	GRA0792076	39	Year(s)	Female Adult	05-May-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHI0792131		Unknown	Female Adult	05-May-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ST 0791916		Unknown	Female Adult	05-May-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUP0792219	48	Year(s)	Female Adult	06-May-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIE0792452		Unknown	Female Adult	07-May-98	BUMPS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAS0792952		Unknown	Female Adult	11-May-98	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUS0792814		Unknown	Female Adult	11-May-98	BLISTERS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPI0792827		Unknown	Female Adult	11-May-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COT0793090		Unknown	Female Adult	12-May-98	DRYNESS	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALL0793474	41	Year(s)	Female Adult	13-May-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ENG0793316	50	Year(s)	Female Adult	13-May-98	REDNESS	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PIO0793369	31	Year(s)	Female Adult	13-May-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHO0793293	47	Year(s)	Female Adult	13-May-98	ACNE	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0793503		Unknown	Unknown	14-May-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POR0793513	45	Year(s)	Female Adult	14-May-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEG0793621		Unknown	Female Adult	14-May-98	CUT	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	MIL0793990	20	Year(s)	Female Adult	18-May-98	N	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COE0793994	29	Year(s)	Female Adult	18-May-98	BUMPS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOF0794272		Unknown	Female Adult	19-May-98	BLISTERS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUC0794587		Unknown	Female Adult	21-May-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAM0794607	28	Year(s)	Female Adult	21-May-98	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAP0794752		Unknown	Unknown	22-May-98	IRRITATION	US	N	EYE	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOR0794951		Unknown	Unknown	26-May-98	PIMPLES	US	Y	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0794985	75	Unknown	Female Adult	26-May-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAS0795311		Unknown	Female Adult	27-May-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRO0795222	50	Year(s)	Female Adult	27-May-98	PIMPLES	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LUS0795552		Unknown	Female Adult	28-May-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COB0795811	42	Year(s)	Female Adult	29-May-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0795666		Unknown	Female Adult	29-May-98	REDNESS	US	Y	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAT0796067		Unknown	Female Adult	01-Jun-98	RASH	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FER0796226		Unknown	Female Adult	02-Jun-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIN0796250	42	Year(s)	Female Adult	02-Jun-98	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOO0796152	36	Year(s)	Female Adult	02-Jun-98	IRRITATION	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOE0796461		Unknown	Unknown	03-Jun-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOR0796413		Unknown	Female Adult	03-Jun-98	PIMPLES	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRA0796657		Unknown	Female Adult	04-Jun-98	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAN0796652		Unknown	Unknown	04-Jun-98	SORENESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAK0796669		Unknown	Female Adult	04-Jun-98	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ARS0796825		Unknown	Female Adult	05-Jun-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHE0796840		Unknown	Female Adult	05-Jun-98	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0796817		Unknown	Unknown	05-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAU0797116		Unknown	Female Adult	08-Jun-98	BLISTERS	CA	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GON0797349	57	Year(s)	Female Adult	09-Jun-98	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AND0797603		Unknown	Female Adult	10-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOT0797552	48	Year(s)	Female Adult	10-Jun-98	ACNE	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0797617		Unknown	Female Adult	10-Jun-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EVA0797823	60	Year(s)	Female Adult	11-Jun-98	RASH	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0798263		Unknown	Female Adult	15-Jun-98	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GLA0798602		Unknown	Female Adult	16-Jun-98	BUMPS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEN0798557		Unknown	Female Adult	16-Jun-98	DRYNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLI0799669		Unknown	Unknown	23-Jun-98	SWELLING	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WES0799617	14	006	Male Child	23-Jun-98	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIN0799754	41	Year(s)	Female Adult	24-Jun-98	BLISTERS	US	N	SKIN	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0800124		Unknown	Female Adult	25-Jun-98	BUMPS	US	N	SKIN	1	Month(s)
OLAY AGE DEFYING RENEWAL CLEANSER	PRE0800351		Unknown	Female Adult	26-Jun-98	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRI0800673		Unknown	Female Adult	29-Jun-98	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MES0800380	60	Year(s)	Female Adult	29-Jun-98	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0800476	74	Year(s)	Female Adult	29-Jun-98	ITCHING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOG0800729		Unknown	Female Adult	30-Jun-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0801174		Unknown	Female Adult	02-Jul-98	SCRATCH	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAI0801522		Unknown	Female Adult	06-Jul-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUC0801812		Unknown	Female Adult	07-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SWI0801805		Unknown	Female Adult	07-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0803142	55	Unknown	Female Adult	13-Jul-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FRA0803082		Unknown	Unknown	13-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0803268		Unknown	Female Adult	14-Jul-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0803391		Unknown	Female Adult	14-Jul-98	PIMPLES	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROD0803223	26	Year(s)	Female Adult	14-Jul-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VER0803245	35	Year(s)	Female Adult	14-Jul-98	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0803616		Unknown	Female Adult	15-Jul-98	BLISTERS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIT0803731		Unknown	Female Adult	16-Jul-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROE0803905		Unknown	Female Adult	16-Jul-98	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VEN0803714		Unknown	Female Adult	16-Jul-98	ITCHING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0805613	48	Year(s)	Female Adult	27-Jul-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	LUD0806003		Unknown	Female Adult	28-Jul-98	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	TRI0806330	51	Year(s)	Female Adult	29-Jul-98	SWELLING	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAY0806625		Unknown	Female Adult	30-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PUC0806687		Unknown	Female Adult	30-Jul-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUL0806891		Unknown	Unknown	31-Jul-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAW0806954		Unknown	Female Adult	31-Jul-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIN0807287	74	Year(s)	Female Adult	03-Aug-98	PIMPLES	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIN0807371		Unknown	Female Adult	04-Aug-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIM0807709	40	Year(s)	Female Adult	05-Aug-98	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAS0808224		Unknown	Unknown	07-Aug-98	IRRITATION	US	N	EYE	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPE0808272	26	Year(s)	Female Adult	07-Aug-98	SWELLING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIE0808090		Unknown	Female Adult	07-Aug-98	BURNING	US	N	EYE	12	Hour(s)
OLAY AGE DEFYING RENEWAL CLEANSER	SCO0808589		Unknown	Female Adult	10-Aug-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0808379	68	Year(s)	Female Adult	10-Aug-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0808298	68	Year(s)	Female Adult	10-Aug-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAS0808348	53	Year(s)	Female Adult	10-Aug-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VOL0808416	59	Year(s)	Female Adult	10-Aug-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ELL0808714	68	Year(s)	Female Adult	11-Aug-98	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0808689	74	Year(s)	Female Adult	11-Aug-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROS0808753		Unknown	Female Adult	11-Aug-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0808681	69	Year(s)	Female Adult	11-Aug-98	BLEEDING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAD0809362	66	Year(s)	Female Adult	13-Aug-98	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0809229		Unknown	Female Adult	13-Aug-98	PIMPLES	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRA0809531		Unknown	Female Adult	14-Aug-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0809904		Unknown	Female Adult	17-Aug-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUN0809665	46	Year(s)	Female Adult	17-Aug-98	CRACKING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GEN0810058		Unknown	Female Adult	18-Aug-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAM0810118	47	Year(s)	Female Adult	18-Aug-98	BURNING	CA	N	SKIN	2	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	JOR0810544	16	Year(s)	Female Child	20-Aug-98	RASH	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DES0810478	58	Year(s)	Female Adult	20-Aug-98	REDNESS	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ENO0810738	48	Year(s)	Female Adult	21-Aug-98	WELTS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	CAM0811082	41	Year(s)	Unknown	24-Aug-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOO0811079		Unknown	Female Adult	24-Aug-98	TINGLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAB0811331		Unknown	Female Adult	25-Aug-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ELL0811669	14	Year(s)	Female Child	26-Aug-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	USS0811607		Unknown	Female Adult	26-Aug-98	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HER0811859	52	Year(s)	Female Adult	27-Aug-98	ITCHING	CA	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUF0811821		Unknown	Female Adult	27-Aug-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EDW0812016		Unknown	Female Adult	28-Aug-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAK0812395	72	Year(s)	Female Adult	01-Sep-98	REDNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ADA0812729		Unknown	Female Adult	02-Sep-98	ACNE	US	N	SKIN	11	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REH0812653	42	Year(s)	Female Adult	02-Sep-98	RASH	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEM0812874	34	Year(s)	Female Adult	03-Sep-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TSI0812876	15	Year(s)	Female Child	03-Sep-98	IRRITATION	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VAL0813070		Unknown	Female Adult	03-Sep-98	DRYNESS	US	N	SKIN	1	Month(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	PAD0813274		Unknown	Female Adult	04-Sep-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ELL0813231		Unknown	Female Adult	04-Sep-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MEL0813246		Unknown	Female Adult	04-Sep-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRO0813326	53	Year(s)	Female Adult	08-Sep-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MEA0813384		Unknown	Female Adult	08-Sep-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	SEA0813905		Unknown	Female Adult	10-Sep-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	O^N0813833		Unknown	Female Adult	10-Sep-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0813914	33	Year(s)	Female Adult	10-Sep-98	BURNING	CA	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	LIN0814001	60	Unknown	Female Adult	11-Sep-98	SCRATCH	US	N	INJURY		
OLAY ASTR LIQ RFRS 7.2 OZ	MON0814085		Unknown	Female Adult	11-Sep-98	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NON0814038		Unknown	Female Adult	11-Sep-98	SWELLING	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WRZ0814169		Unknown	Female Adult	11-Sep-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUT0814258		Unknown	Female Adult	14-Sep-98	WELTS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TRO0814338		Unknown	Female Adult	14-Sep-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EDE0814474	32	Year(s)	Female Adult	15-Sep-98	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	FEN0814702		Unknown	Female Adult	16-Sep-98	BURNING	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	PHI0814856	44	Year(s)	Female Adult	16-Sep-98	BLISTERS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAR0814811		Unknown	Female Adult	16-Sep-98	BLISTERS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FOS0814997		Unknown	Female Adult	17-Sep-98	SWELLING	US	N	EYE INDIRECT	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAS0815146		Unknown	Female Adult	18-Sep-98	SWELLING	US	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SOF0815107		Unknown	Female Adult	18-Sep-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0815058		Unknown	Female Adult	18-Sep-98	REDNESS	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEL0815510	25	Year(s)	Female Adult	21-Sep-98	REDNESS	CA	N	SKIN	15	Minute(s)
OLAY AGE DEFYING RENEWAL CLEANSER	DRA0816471		Unknown	Male Adult	28-Sep-98	STINGING	US	N	EYE	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRI0816539	74	Year(s)	Female Adult	28-Sep-98	HEADACHE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LYN0816410		Unknown	Female Adult	28-Sep-98	CUT	US	N	INJURY		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AND0816925	42	Year(s)	Female Adult	30-Sep-98	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0817330		Unknown	Unknown	02-Oct-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YAL0817190	45	Year(s)	Female Adult	02-Oct-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0817393		Unknown	Female Adult	05-Oct-98	COUGHING	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLE0817689		Unknown	Female Adult	06-Oct-98	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0817754		Unknown	Female Adult	06-Oct-98	RASH	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FUL0818030	30	Year(s)	Female Adult	07-Oct-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LUT0818520	34	Year(s)	Female Adult	12-Oct-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROV0818649		Unknown	Female Adult	12-Oct-98	N	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0818455		Unknown	Female Adult	12-Oct-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALI0818808	52	Year(s)	Female Adult	13-Oct-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEA0818730		Unknown	Female Adult	13-Oct-98	IRRITATION	US	Y	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAR0818836	70	Year(s)	Female Adult	13-Oct-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RYA0818694	52	Year(s)	Female Adult	13-Oct-98	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRE0819137	76	Year(s)	Female Adult	15-Oct-98	BURNING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALD0819361	63	Year(s)	Female Adult	16-Oct-98	RASH	CA	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ISA0819578	62	Year(s)	Female Adult	19-Oct-98	IRRITATION	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OBL0819557		Unknown	Female Adult	19-Oct-98	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0820097		Unknown	Female Adult	21-Oct-98	N	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0820044	35	Year(s)	Female Adult	21-Oct-98	PIMPLES	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PUG0820653		Unknown	Female Adult	23-Oct-98	PIMPLES	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BRO0820764	70	Year(s)	Female Adult	26-Oct-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COU0820838	58	Year(s)	Female Adult	26-Oct-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REY0820871		Unknown	Female Adult	26-Oct-98	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAB0821762	57	Year(s)	Female Adult	30-Oct-98	REDNESS	US	N	SKIN	48	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	QUI0821700	52	Year(s)	Female Adult	30-Oct-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DYS0821881	75	Year(s)	Female Adult	02-Nov-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STE0822004	31	Year(s)	Female Adult	02-Nov-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0822328	26	Year(s)	Female Adult	03-Nov-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIK0822236	64	Year(s)	Female Adult	03-Nov-98	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRI0822501		Unknown	Female Adult	04-Nov-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAG0822393	70	Year(s)	Female Adult	04-Nov-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0822696	37	Year(s)	Female Adult	05-Nov-98	RASH	US	N	SKIN	48	Hour(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CON0822586	70	Year(s)	Female Adult	05-Nov-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CUM0822713		Unknown	Female Adult	05-Nov-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TIM0822590	61	Year(s)	Female Adult	05-Nov-98	DRYNESS	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCM0822811		Unknown	Female Adult	06-Nov-98	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALE0823190	34	Year(s)	Female Adult	09-Nov-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0823088		Unknown	Female Adult	09-Nov-98	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0823538		Unknown	Female Adult	10-Nov-98	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MEN0823568	50	Year(s)	Female Adult	10-Nov-98	HIVES	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0823740	35	Year(s)	Female Adult	11-Nov-98	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STA0823752		Unknown	Female Adult	11-Nov-98	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	BRO0824172		Unknown	Female Adult	13-Nov-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOM0824083	62	Year(s)	Female Adult	13-Nov-98	IRRITATION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GEL0824134		Unknown	Female Adult	13-Nov-98	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0824915	34	Year(s)	Female Adult	18-Nov-98	DRYNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOD0825091		Unknown	Female Adult	18-Nov-98	DERMATITIS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOL0824910	70	Year(s)	Female Adult	18-Nov-98	OTHER	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LUI0825375		Unknown	Unknown	20-Nov-98	IRRITATION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0825460	43	Year(s)	Female Adult	20-Nov-98	SWELLING	US	N	SKIN	9	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COR0825532		Unknown	Female Adult	23-Nov-98	SWELLING	US	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0825892		Unknown	Female Adult	24-Nov-98	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HER0826196		Unknown	Female Adult	25-Nov-98	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YOU0826081	58	Year(s)	Female Adult	25-Nov-98	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEA0826512		Unknown	Female Adult	30-Nov-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FRO0826475	24	Year(s)	Female Adult	30-Nov-98	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUE0826462	40	Year(s)	Female Adult	30-Nov-98	ITCHING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAM0826782		Unknown	Female Adult	01-Dec-98	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEL0827277		Unknown	Female Adult	03-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0827499		Unknown	Unknown	04-Dec-98	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0827514		Unknown	Female Adult	04-Dec-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOU0827831		Unknown	Female Adult	07-Dec-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAD0827732	28	Year(s)	Female Adult	07-Dec-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOS0828108	66	Year(s)	Female Adult	09-Dec-98	BURNING	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LUT0828274	32	Year(s)	Female Adult	09-Dec-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROS0828171		Unknown	Female Adult	09-Dec-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DIC0828593		Unknown	Female Adult	11-Dec-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCC0828511	38	Year(s)	Female Adult	11-Dec-98	FLAKING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DIC0828684		Unknown	Female Adult	14-Dec-98	ACNE	US	N	SKIN	7	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIF0828652	51	Year(s)	Female Adult	14-Dec-98	RASH	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0828955		Unknown	Female Adult	14-Dec-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0828689		Unknown	Female Adult	14-Dec-98	FLAKING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIE0828742		Unknown	Female Adult	14-Dec-98	DRYNESS	US	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0828727	54	Year(s)	Female Adult	14-Dec-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOL0829183	58	Year(s)	Female Adult	16-Dec-98	PIMPLES	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCK0829366		Unknown	Female Adult	17-Dec-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOS0829799	38	Year(s)	Female Adult	21-Dec-98	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUT0829918		Unknown	Female Adult	21-Dec-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ORT0829939		Unknown	Female Adult	21-Dec-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUM0830135	51	Year(s)	Female Adult	22-Dec-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAP0830251		Unknown	Female Adult	23-Dec-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEA0830606		Unknown	Unknown	28-Dec-98	BURNING	US	N	SKIN	1	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NEN0830367		Unknown	Unknown	28-Dec-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0830821		Unknown	Female Adult	29-Dec-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOL0830810	19	Year(s)	Female Adult	29-Dec-98	BUMPS	US	N	SKIN	3	Week(s)
OLAY FOAMING FACE WASH SENSITIVE SIZE ND	LAI0830855		Unknown	Female Adult	29-Dec-98	BURNING	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	CRY0831046		Unknown	Female Adult	30-Dec-98	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEJ0831037	16	Year(s)	Female Child	30-Dec-98	RASH	US	Y	SKIN	15	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOO0831013		Unknown	Female Adult	30-Dec-98	RAW	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NOR0831070	18	Year(s)	Female Adult	30-Dec-98	RASH	US	N	SKIN	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0831311	53	Year(s)	Female Adult	04-Jan-99	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRU0831465		Unknown	Female Adult	04-Jan-99	PEELING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIV0831176		Unknown	Female Adult	04-Jan-99	PEELING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0831799		Unknown	Female Adult	05-Jan-99	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0831557		Unknown	Female Adult	05-Jan-99	PIMPLES	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0831822		Unknown	Female Adult	06-Jan-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DRU0831859	42	Year(s)	Female Adult	06-Jan-99	BLISTERS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OWE0832025		Unknown	Female Adult	06-Jan-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PRI0832018		Unknown	Female Adult	06-Jan-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0832355		Unknown	Female Adult	08-Jan-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAL0832364		Unknown	Female Adult	08-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRA0832735	48	Year(s)	Female Adult	11-Jan-99	REDNESS	US	N	EYE	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAT0832887	79	Year(s)	Female Adult	12-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POK0833077		Unknown	Female Adult	12-Jan-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0833100	41	Year(s)	Female Adult	13-Jan-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAR0833219		Unknown	Female Adult	13-Jan-99	DRYNESS	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRE0833206		Unknown	Female Adult	13-Jan-99	ITCHING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REE0833180		Unknown	Female Adult	13-Jan-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0833433		Unknown	Female Adult	14-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUD0833686		Unknown	Female Adult	15-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOU0833499		Unknown	Female Adult	15-Jan-99	CUT	US	N	INJURY		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIC0833667	44	Year(s)	Female Adult	15-Jan-99	BURNING	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STE0833598	64	Year(s)	Female Adult	15-Jan-99	REDNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LIL0833886		Unknown	Female Adult	19-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0833948		Unknown	Female Adult	19-Jan-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEA0834166	52	Year(s)	Female Adult	20-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0834257	48	Year(s)	Female Adult	20-Jan-99	HIVES	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0834171	70	Year(s)	Female Adult	20-Jan-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOW0834404		Unknown	Female Adult	21-Jan-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YAR0834602		Unknown	Female Adult	22-Jan-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	KIN0834898		Unknown	Female Adult	25-Jan-99	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AMA0834878		Unknown	Female Adult	25-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COF0835136	53	Year(s)	Female Adult	25-Jan-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOW0834814		Unknown	Female Adult	25-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAY0834882		Unknown	Female Adult	25-Jan-99	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0835363		Unknown	Female Adult	26-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0835215	65	Year(s)	Female Adult	26-Jan-99	PIMPLES	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIN0835429		Unknown	Female Adult	27-Jan-99	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AND0835883		Unknown	Female Adult	29-Jan-99	SWELLING	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOE0835880	58	Year(s)	Female Adult	29-Jan-99	DRYNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MER0836162	32	Year(s)	Female Adult	01-Feb-99	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0836502		Unknown	Female Adult	02-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0836459		Unknown	Female Adult	02-Feb-99	ITCHING	US	N	SKIN	1	Day(s)
OLAY FFW LOT SEN 6.78 OZ	SEF0836617		Unknown	Female Adult	02-Feb-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAC0836716	44	Year(s)	Female Adult	03-Feb-99	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAM0837146		Unknown	Female Adult	05-Feb-99	DRYNESS	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0837250		Unknown	Female Adult	05-Feb-99	RASH	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	SAN0837547	33	Year(s)	Female Adult	08-Feb-99	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DYS0837509	76	Year(s)	Female Adult	08-Feb-99	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEC0837497		Unknown	Female Adult	08-Feb-99	PEELING	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0837678		Unknown	Female Adult	08-Feb-99	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZAC0837482		Unknown	Female Adult	08-Feb-99	RASH	US	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAR0837920		Unknown	Female Adult	10-Feb-99	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOS0837959		Unknown	Female Adult	10-Feb-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZUL0837918		Unknown	Female Adult	10-Feb-99	SWELLING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0838153		Unknown	Female Adult	11-Feb-99	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOY0838387		Unknown	Unknown	12-Feb-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEI0838943		Unknown	Female Adult	17-Feb-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEI0838937		Unknown	Female Adult	17-Feb-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0839306		Unknown	Female Adult	18-Feb-99	FLAKING	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0839300		Unknown	Unknown	18-Feb-99	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOR0839334		Unknown	Female Adult	18-Feb-99	BURNING	US	N	EYE		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOL0839375	22	Year(s)	Female Adult	18-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEA0840066		Unknown	Female Adult	23-Feb-99	BURNING	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	BUR0840297		Unknown	Female Adult	24-Feb-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAM0840385		Unknown	Female Adult	24-Feb-99	ROUGH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YAN0840331		Unknown	Female Adult	24-Feb-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CER0840765		Unknown	Female Adult	26-Feb-99	PIMPLES	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MUL0840785		Unknown	Female Adult	26-Feb-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	THO0841172	68	Year(s)	Female Adult	01-Mar-99	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JAS0841037		Unknown	Female Adult	01-Mar-99	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0841040		Unknown	Female Adult	01-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DOM0841411		Unknown	Unknown	02-Mar-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY FFW LOT SEN 6.78 OZ	SNY0841476		Unknown	Unknown	02-Mar-99	PIMPLES	US	N	SKIN	3	Week(s)
OLAY FACIAL CLEANSING LOTION SIZE ND	SIR0841730		Unknown	Female Adult	03-Mar-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAR0842214	45	Year(s)	Female Adult	05-Mar-99	HIVES	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WHI0842206		Unknown	Unknown	05-Mar-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAY0842696		Unknown	Female Adult	08-Mar-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THO0842785		Unknown	Female Adult	09-Mar-99	IRRITATION	US	N	EYE		
OLAY AGE DEFYING RENEWAL CLEANSER	FOU0843064		Unknown	Female Adult	10-Mar-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DE 0843329	68	Year(s)	Female Adult	11-Mar-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0843491		Unknown	Female Adult	11-Mar-99	N	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOS0843566		Unknown	Female Adult	12-Mar-99	TEARING	US	N	EYE INDIRECT	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRE0844037	15	Year(s)	Female Adult	15-Mar-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REA0844046		Unknown	Female Adult	15-Mar-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0843922	62	Year(s)	Female Adult	15-Mar-99	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAL0844671	36	Year(s)	Female Adult	17-Mar-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEB0844487		Unknown	Female Adult	17-Mar-99	CONGESTION	US	N	INHALATION	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0844744		Unknown	Female Adult	18-Mar-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOA0845102		Unknown	Female Adult	19-Mar-99	STINGING	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOC0844976		Unknown	Female Adult	19-Mar-99	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MED0845373		Unknown	Female Adult	22-Mar-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JAK0845730	35	Year(s)	Female Adult	23-Mar-99	REDNESS	US	Y	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAI0846047		Unknown	Female Adult	24-Mar-99	VISION	US	N	EYE	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEL0845912		Unknown	Female Child	24-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WOR0845973		Unknown	Female Adult	24-Mar-99	DRYNESS	US	N	SKIN	6	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JEN0846274		Unknown	Female Adult	25-Mar-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FOR0846626		Unknown	Female Adult	29-Mar-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAF0846592		Unknown	Female Adult	29-Mar-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PHI0846747		Unknown	Female Adult	29-Mar-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0846998		Unknown	Female Adult	30-Mar-99	REACTION	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAT0846994	59	Year(s)	Female Adult	30-Mar-99	CHAPPED	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUN0847464	45	Year(s)	Female Adult	31-Mar-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCC0847216		Unknown	Unknown	31-Mar-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TOR0847662		Unknown	Female Adult	01-Apr-99	DRYNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	YEP0847717	44	Year(s)	Female Adult	05-Apr-99	PIMPLES	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0847750		Unknown	Female Adult	05-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0847946		Unknown	Female Adult	05-Apr-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0847700		Unknown	Female Adult	05-Apr-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0848262		Unknown	Female Adult	07-Apr-99	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAN0848633		Unknown	Female Adult	08-Apr-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEP0848718		Unknown	Female Adult	09-Apr-99	BUMPS	US	N	SKIN		
OLAY FACIAL CLEANSING LOTION SIZE ND	BRA0848800		Unknown	Female Adult	09-Apr-99	STINGING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALW0849270		Unknown	Female Adult	12-Apr-99	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STI0849011		Unknown	Female Adult	12-Apr-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIR0849367	41	Year(s)	Female Adult	13-Apr-99	REDNESS	CA	N	SKIN		Unknown
AGE DEFYING SERIES CLEANSER PACKETTE	ROC0850060		Unknown	Female Adult	16-Apr-99	BURNING	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ARN0850175		Unknown	Unknown	16-Apr-99	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TRU0850143	32	Year(s)	Female Adult	16-Apr-99	BLISTERS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	MUL0850459	26	Year(s)	Female Adult	19-Apr-99	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ATH0850538		Unknown	Female Adult	19-Apr-99	BURNING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUI0850553		Unknown	Female Adult	19-Apr-99	ITCHING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHR0851421		Unknown	Female Adult	23-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0851334		Unknown	Female Adult	23-Apr-99	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CON0851833		Unknown	Female Adult	26-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0851732		Unknown	Female Adult	26-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	AME0851891		Unknown	Female Adult	27-Apr-99	BUMPS	US	N	SKIN	1	Month(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAG0852062		Unknown	Female Adult	27-Apr-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHO0852305	32	Year(s)	Female Adult	28-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GHI0852242		Unknown	Female Adult	28-Apr-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	MAG0852480	17	Year(s)	Female Adult	29-Apr-99	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	YOU0852406		Unknown	Female Adult	29-Apr-99	PEELING	US	N	SKIN	1	Year(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCO0853129		Unknown	Female Adult	04-May-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEW0853653		Unknown	Female Adult	06-May-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAH0853866		Unknown	Female Adult	07-May-99	HIVES	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	ELL0854023		Unknown	Female Adult	10-May-99	SNEEZING	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	SCH0854360		Unknown	Female Adult	11-May-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0854369	47	Year(s)	Female Adult	11-May-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEL0854447	16	Year(s)	Female Child	11-May-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KRE0854765		Unknown	Female Adult	13-May-99	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAC0855109		Unknown	Female Adult	14-May-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHE0855052		Unknown	Female Adult	14-May-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROY0855263		Unknown	Female Adult	17-May-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GEO0855551	38	Year(s)	Female Adult	18-May-99	ACNE	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0855536		Unknown	Female Adult	18-May-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUB0855827	72	Year(s)	Female Adult	19-May-99	REDNESS	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAJ0856022		Unknown	Female Adult	20-May-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VIE0856367		Unknown	Female Adult	21-May-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIN0856480		Unknown	Female Adult	24-May-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VIC0856695		Unknown	Female Adult	24-May-99	PIMPLES	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WHE0856673		Unknown	Female Adult	24-May-99	BURNING	US	Y	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COC0856971		Unknown	Female Adult	25-May-99	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0856825		Unknown	Female Adult	25-May-99	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOM0857568		Unknown	Female Adult	28-May-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPE0857914		Unknown	Female Adult	01-Jun-99	SWELLING	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	CHE0858209		Unknown	Female Adult	02-Jun-99	WELTS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUT0858157		Unknown	Female Adult	02-Jun-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAG0858326		Unknown	Female Adult	03-Jun-99	BUMPS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIE0858563		Unknown	Female Adult	04-Jun-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAN0859141		Unknown	Female Adult	08-Jun-99	RASH	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CLEANSER PACKETTE	MAG0859440		Unknown	Unknown	09-Jun-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIT0859906		Unknown	Female Adult	11-Jun-99	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ZEM0859818		Unknown	Female Adult	11-Jun-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUW0860031		Unknown	Female Adult	14-Jun-99	SWELLING	US	N	EYE INDIRECT	4	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0859987		Unknown	Female Adult	14-Jun-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	3		Unknown	Female Adult	14-Jun-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WEL0860000		Unknown	Female Adult	14-Jun-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CON0860249	15	Year(s)	Male Child	15-Jun-99	DRYNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAL0860465		Unknown	Female Adult	15-Jun-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0860604		Unknown	Female Adult	16-Jun-99	ITCHING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0860757	51	Year(s)	Female Adult	17-Jun-99	ROUGH	US	N	SKIN	2	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAV0861018		Unknown	Male Adult	18-Jun-99	OTHER	US	N	ORAL/NASAL		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TUR0861422		Unknown	Unknown	22-Jun-99	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0861969		Unknown	Female Adult	24-Jun-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0862340		Unknown	Female Adult	28-Jun-99	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CLI0862742		Unknown	Female Adult	29-Jun-99	BUMPS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0863077		Unknown	Female Adult	01-Jul-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HUG0863521		Unknown	Female Adult	06-Jul-99	BURNING	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEA0863798		Unknown	Female Adult	07-Jul-99	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIZ0864734		Unknown	Female Adult	13-Jul-99	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	IBR0865281		Unknown	Female Adult	16-Jul-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REI0865943		Unknown	Female Adult	21-Jul-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAP0866365	73	Year(s)	Female Adult	23-Jul-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALE0866793		Unknown	Female Adult	26-Jul-99	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOR0866696	60	Year(s)	Female Adult	26-Jul-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	UTT0866731		Unknown	Female Adult	26-Jul-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KNO0866832	33	Year(s)	Female Adult	27-Jul-99	PIMPLES	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CLEANSER	NON0867159		Unknown	Female Adult	29-Jul-99	REDNESS	US	N	INGESTION		Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KEY0867165		Unknown	Female Adult	29-Jul-99	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PUE0867311		Unknown	Male Adult	29-Jul-99	BUMPS	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOL0867974		Unknown	Female Adult	03-Aug-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WER0867885		Unknown	Female Adult	03-Aug-99	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NEA0868649		Unknown	Female Adult	09-Aug-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAJ0868755		Unknown	Female Adult	09-Aug-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRA0869625		Unknown	Female Adult	13-Aug-99	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0869773	29	Year(s)	Female Adult	16-Aug-99	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NOR0869893		Unknown	Female Adult	16-Aug-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIM0869700		Unknown	Female Adult	16-Aug-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEI0870306	65	Year(s)	Female Adult	19-Aug-99	ITCHING	CA	N	EYE INDIRECT	3	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	CAP0870432		Unknown	Female Adult	20-Aug-99	REACTION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEA0870495		Unknown	Female Adult	20-Aug-99	STINGING	US	N	SKIN	2	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0870555		Unknown	Female Adult	20-Aug-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCO0870552		Unknown	Female Adult	20-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FRE0870676		Unknown	Female Adult	23-Aug-99	ITCHING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0871099		Unknown	Female Adult	24-Aug-99	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COW0870921		Unknown	Female Adult	24-Aug-99	IRRITATION	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRU0871145		Unknown	Female Adult	25-Aug-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAW0871229		Unknown	Female Adult	25-Aug-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SIM0871485	82	Year(s)	Female Adult	26-Aug-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEB0871715	42	Year(s)	Female Adult	27-Aug-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0871648		Unknown	Female Adult	27-Aug-99	PIMPLES	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOR0871730	41	Year(s)	Female Adult	30-Aug-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RYA0871819		Unknown	Unknown	30-Aug-99	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROU0872076	63	Year(s)	Female Adult	31-Aug-99	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOU0872285		Unknown	Female Adult	01-Sep-99	BUMPS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NG0872201	30	Year(s)	Female Adult	01-Sep-99	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0872539	25	Year(s)	Female Adult	02-Sep-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOL0872505		Unknown	Female Adult	02-Sep-99	TINGLING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SOB0872405		Unknown	Female Adult	02-Sep-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	NAB0872727		Unknown	Female Adult	03-Sep-99	VISION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAG0872856		Unknown	Female Adult	07-Sep-99	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ORN0872830		Unknown	Female Adult	07-Sep-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0873341		Unknown	Female Adult	09-Sep-99	REDNESS	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0873686		Unknown	Female Adult	10-Sep-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PET0873639		Unknown	Female Adult	10-Sep-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SMI0874016		Unknown	Female Adult	13-Sep-99	SWELLING	US	N	EYE INDIRECT	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ARE0874248		Unknown	Female Adult	14-Sep-99	BURNING	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEA0874123		Unknown	Female Adult	14-Sep-99	REDNESS	US	N	SKIN	3	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CHU0874053		Unknown	Unknown	14-Sep-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MUN0874414		Unknown	Female Adult	15-Sep-99	PIMPLES	US	N	SKIN	14	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LA 0874459		Unknown	Female Adult	16-Sep-99	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOE0874674		Unknown	Unknown	17-Sep-99	SORENESS	US	N	SKIN	8	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	SHA0874997	36	Year(s)	Female Adult	20-Sep-99	ITCHING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BES0875590	81	Year(s)	Female Adult	23-Sep-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THO0876497		Unknown	Female Adult	29-Sep-99	RASH	US	N	SKIN	7	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	MON0876643		Unknown	Female Adult	30-Sep-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAB0876655		Unknown	Female Adult	30-Sep-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROS0876608		Unknown	Female Adult	30-Sep-99	RASH	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MC 0876969		Unknown	Female Adult	04-Oct-99	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NOD0877434		Unknown	Female Adult	05-Oct-99	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	VAN0877759	3	Year(s)	Male Child	07-Oct-99	NONE	CA	N	INGESTION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAL0878066		Unknown	Female Adult	11-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0878756		Unknown	Female Adult	13-Oct-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GIO0879109		Unknown	Female Adult	15-Oct-99	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STE0879036		Unknown	Female Adult	15-Oct-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEP0879275		Unknown	Female Adult	18-Oct-99	SCRATCH	US	N	EYE	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	PHI0879458	83	Year(s)	Female Adult	19-Oct-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ARN0879595		Unknown	Female Adult	19-Oct-99	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAL0879424	30	Year(s)	Female Adult	19-Oct-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0879793		Unknown	Female Adult	20-Oct-99	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	EVA0879922		Unknown	Female Adult	21-Oct-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0880191		Unknown	Female Adult	25-Oct-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUB0880800	53	Year(s)	Female Adult	28-Oct-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOP0881081		Unknown	Female Adult	29-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THI0881105	60	Year(s)	Female Adult	29-Oct-99	DRYNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	DAV0881325	61	Year(s)	Male Adult	01-Nov-99	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	SPI0882130		Unknown	Female Adult	05-Nov-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PEA0882322		Unknown	Female Adult	08-Nov-99	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	P L0883097		Unknown	Female Adult	11-Nov-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PRO0883104		Unknown	Female Adult	11-Nov-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	KOE0883345		Unknown	Female Adult	12-Nov-99	STINGING	US	N	SKIN	10	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FEL0883879		Unknown	Female Adult	17-Nov-99	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHR0884213		Unknown	Female Adult	18-Nov-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOO0885094	76	Year(s)	Female Adult	24-Nov-99	PIMPLES	US	N	SKIN	10	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	REF0886178		Unknown	Unknown	03-Dec-99	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER	PAD0886330	46	Year(s)	Female Adult	06-Dec-99	SWELLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GAR0886191		Unknown	Female Adult	06-Dec-99	BURNING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PHI0886205		Unknown	Female Adult	06-Dec-99	DRYNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KYL0886726		Unknown	Female Adult	08-Dec-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIV0886785		Unknown	Female Adult	08-Dec-99	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROM0886812		Unknown	Female Adult	08-Dec-99	OTHER	US	N	SKIN	1	Year(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIE0887058		Unknown	Female Adult	10-Dec-99	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KID0887219	72	Year(s)	Female Adult	13-Dec-99	SORENESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SLE0887274		Unknown	Female Adult	13-Dec-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOU0887470		Unknown	Female Adult	14-Dec-99	BURNING	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	JOH0887662		Unknown	Female Adult	15-Dec-99	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIR0887779		Unknown	Female Adult	16-Dec-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MEN0888228		Unknown	Female Adult	20-Dec-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0888519	76	Year(s)	Female Adult	22-Dec-99	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BON0888761	26	Year(s)	Female Adult	27-Dec-99	REDNESS	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ADA0888979	40	Year(s)	Female Adult	28-Dec-99	BUMPS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KLE0888966		Unknown	Female Adult	28-Dec-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CUN0889591		Unknown	Female Adult	04-Jan-00	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLE0889594		Unknown	Female Adult	04-Jan-00	BUMPS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAL0889643	39	Year(s)	Female Adult	04-Jan-00	REDNESS	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COU0889907		Unknown	Female Adult	05-Jan-00	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAR0890203		Unknown	Female Adult	07-Jan-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GET0890598		Unknown	Female Adult	10-Jan-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0890693	74	Year(s)	Female Adult	11-Jan-00	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0891128		Unknown	Female Adult	13-Jan-00	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FOW0891154		Unknown	Female Adult	13-Jan-00	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAN0891041		Unknown	Female Adult	13-Jan-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CAM0891273		Unknown	Female Adult	14-Jan-00	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NOV0891262		Unknown	Female Adult	14-Jan-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEB0891415		Unknown	Female Adult	17-Jan-00	BUMPS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEU0891408	43	Year(s)	Female Adult	17-Jan-00	RASH	CA	N	SKIN	4	Day(s)
AGE DEFYING SERIES CLEANSER PACKETTE	SIN0891558		Unknown	Female Adult	18-Jan-00	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HYI0891799		Unknown	Female Adult	19-Jan-00	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BER0891863		Unknown	Female Adult	20-Jan-00	RASH	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOO0892017		Unknown	Female Adult	20-Jan-00	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CUL0892115	51	Year(s)	Female Adult	21-Jan-00	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAT0892151		Unknown	Female Adult	21-Jan-00	ACNE	US	N	SKIN		
OLAY FACIAL CLEANSING LOTION SIZE ND	ROB0892286		Unknown	Unknown	24-Jan-00	TEARING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIT0892716		Unknown	Female Adult	25-Jan-00	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NOR0892504		Unknown	Female Adult	25-Jan-00	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	O^B0892720		Unknown	Male Adult	25-Jan-00	OTHER	US	N	SKIN	3.5	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PRI0892696	44	Year(s)	Female Adult	25-Jan-00	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROT0892557		Unknown	Female Adult	25-Jan-00	STINGING	US	N	EYE	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	STO0892825	65	Year(s)	Female Adult	26-Jan-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIL0893148	33	Year(s)	Female Adult	28-Jan-00	ITCHING	CA	N	EYE	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUO0893412		Unknown	Female Adult	31-Jan-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUB0893566	28	Year(s)	Female Adult	31-Jan-00	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAC0893783		Unknown	Female Adult	01-Feb-00	BURNING	US	N	SKIN	2	Week(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WIG0893761		Unknown	Female Adult	01-Feb-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAI0893954		Unknown	Female Adult	02-Feb-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOP0893927	32	Year(s)	Female Adult	02-Feb-00	BURNING	US	N	SKIN	14	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIC0894385		Unknown	Female Adult	04-Feb-00	BURNING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUE0894402		Unknown	Female Adult	04-Feb-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOV0894616	52	Year(s)	Female Adult	07-Feb-00	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LOY0894529		Unknown	Female Adult	07-Feb-00	PIMPLES	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAF0894877	28	Year(s)	Female Adult	08-Feb-00	PIMPLES	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BEL0895142		Unknown	Female Adult	09-Feb-00	PEELING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOH0895311		Unknown	Female Adult	10-Feb-00	ACNE	US	N	SKIN	1	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TRU0895340		Unknown	Female Adult	10-Feb-00	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAV0895542	66	Year(s)	Female Adult	11-Feb-00	REDNESS	CA	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FER0895942	22	Year(s)	Female Adult	14-Feb-00	PEELING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIL0895815		Unknown	Female Adult	14-Feb-00	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KIR0895882	38	Year(s)	Female Adult	14-Feb-00	RASH	CA	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	BIC0896432	67	Year(s)	Female Adult	16-Feb-00	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAY0896351		Unknown	Female Adult	16-Feb-00	RASH	CA	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RED0896658		Unknown	Female Adult	17-Feb-00	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JON0897560		Unknown	Female Adult	25-Feb-00	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COC0899258		Unknown	Female Adult	08-Mar-00	ITCHING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HER0899445		Unknown	Female Adult	08-Mar-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	REE0899347	36	Year(s)	Female Adult	08-Mar-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	HOU0899964	70	Year(s)	Female Adult	13-Mar-00	SWELLING	US	N	EYE INDIRECT	3	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0900718		Unknown	Female Adult	17-Mar-00	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MES0900704	39	Year(s)	Female Adult	17-Mar-00	REDNESS	US	N	SKIN	10	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAM0900770	36	Year(s)	Female Adult	17-Mar-00	HIVES	US	N	SKIN	30	Minute(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HEI0901111		Unknown	Female Adult	21-Mar-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIS0901214		Unknown	Female Adult	21-Mar-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIT0901185	59	Year(s)	Female Adult	21-Mar-00	ATTACK	US	N	INHALATION		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROB0901439		Unknown	Female Adult	22-Mar-00	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KOV0901581		Unknown	Female Adult	23-Mar-00	REDNESS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	HAL0901773		Unknown	Female Adult	24-Mar-00	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DAV0901767		Unknown	Female Adult	24-Mar-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUC0902108	68	Year(s)	Female Adult	27-Mar-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FLO0902114		Unknown	Female Adult	27-Mar-00	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIP0902217		Unknown	Female Adult	28-Mar-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0902173		Unknown	Female Adult	28-Mar-00	REDNESS	US	N	SKIN		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SEA0902474		Unknown	Female Adult	29-Mar-00	OTHER	US	N	SKIN	4	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0902487	34	Year(s)	Female Adult	29-Mar-00	RAW	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KRY0902613		Unknown	Female Adult	30-Mar-00	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAN0902621		Unknown	Female Adult	30-Mar-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROL0902683		Unknown	Female Adult	30-Mar-00	PEELING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	POE0902799		Unknown	Female Adult	31-Mar-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FAG0903341		Unknown	Female Adult	04-Apr-00	BURNING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER	UNK0903454		Unknown	Unknown	05-Apr-00	FLAKING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DUR0903431		Unknown	Female Adult	05-Apr-00	ACNE	US	Y	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COM0904100		Unknown	Female Adult	10-Apr-00	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GRA0903909	78	Year(s)	Female Adult	10-Apr-00	REDNESS	CA	N	SKIN	10	Hour(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAR0904342		Unknown	Female Adult	12-Apr-00	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	CRA0904595		Unknown	Female Adult	13-Apr-00	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BIT0904797		Unknown	Female Adult	14-Apr-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GOL0904670	14	Year(s)	Female Adult	14-Apr-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	OLD0904816		Unknown	Female Adult	17-Apr-00	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	GUN0905285		Unknown	Female Adult	19-Apr-00	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ALL0905594		Unknown	Female Adult	24-Apr-00	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAL0905664	35	Year(s)	Female Adult	24-Apr-00	BUMPS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAD0905875	77	Year(s)	Female Adult	25-Apr-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0905890	35	Year(s)	Female Adult	25-Apr-00	REDNESS	CA	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RAY0906001		Unknown	Female Adult	25-Apr-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	TAN0906174		Unknown	Female Adult	26-Apr-00	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ERI0906334		Unknown	Female Adult	27-Apr-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HAM0906397		Unknown	Unknown	27-Apr-00	PEELING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	KAB0906904		Unknown	Female Adult	02-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0907158		Unknown	Female Adult	03-May-00	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIC0907199		Unknown	Female Adult	03-May-00	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RUG0907092		Unknown	Female Adult	03-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PIK0907395		Unknown	Female Adult	04-May-00	BLISTERS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COS0907807		Unknown	Female Adult	08-May-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RIB0908119		Unknown	Female Adult	10-May-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAR0908442		Unknown	Female Adult	12-May-00	DRYNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	NIE0909406		Unknown	Female Adult	19-May-00	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	ROM0909263	49	Year(s)	Female Adult	19-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCH0909912		Unknown	Female Adult	24-May-00	IRRITATION	US	Y	EYE INDIRECT		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIS0910077		Unknown	Female Adult	25-May-00	NAUSEA	US	N	INHALATION		

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JOH0910272	72	Year(s)	Female Adult	26-May-00	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LEI0910594	30	Year(s)	Female Adult	30-May-00	PIMPLES	US	N	SKIN	1.5	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0910806		Unknown	Female Adult	31-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BUD0911090		Unknown	Female Adult	02-Jun-00	RASH	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLE0911375		Unknown	Female Adult	05-Jun-00	BUMPS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	FIN0911805	69	Year(s)	Female Adult	08-Jun-00	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HIL0911896		Unknown	Female Adult	08-Jun-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LET0912537		Unknown	Female Adult	13-Jun-00	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0912585		Unknown	Female Adult	14-Jun-00	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCA0913386	76	Year(s)	Female Adult	21-Jun-00	IRRITATION	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0913324		Unknown	Female Adult	21-Jun-00	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DIN0914229		Unknown	Male Adult	29-Jun-00	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DON0914482		Unknown	Female Adult	03-Jul-00	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	THO0914988		Unknown	Unknown	07-Jul-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	UNK0916654			006	25-Jul-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	JAC0916627	31	Year(s)	Female Adult	25-Jul-00	PIMPLES	CA	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	THO0917189			006	28-Jul-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	STA0917502			006	31-Jul-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	KAU0918020	40	Year(s)	Female Adult	03-Aug-00	BURNING	US	N	EYE		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	REI0918494			006	08-Aug-00	ACNE	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	UNK0918492			006	08-Aug-00	ACNE	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	BUI0918678	47	Year(s)	Female Adult	10-Aug-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BAC0918834	23	Year(s)	Female Adult	10-Aug-00	REDNESS	US	Y	EYE		
AGE DEFYING SERIES CLEANSER PACKETTE	AUL0919418				16-Aug-00	OTHER	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PAR0920005			006	21-Aug-00	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	HOL0920828	22	Year(s)	Female Adult	28-Aug-00	FLAKING	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	MOW0921338			999	31-Aug-00	UNKNOWN	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BRO0922342			006	11-Sep-00	WRINKLES	US	N	SKIN	2	Month(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAV0922846			006	14-Sep-00	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPE0922861	33	Year(s)	Female Adult	14-Sep-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIN0923126			006	15-Sep-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	WEB0924488	30	Year(s)	Female Adult	26-Sep-00	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIT0924669			006	26-Sep-00	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SAL0925211	28	Year(s)	Female Adult	29-Sep-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	SAL0925457	50	Year(s)	Female Adult	02-Oct-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	COL0925500	42	Year(s)	Female Adult	02-Oct-00	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	LEE0925821			006	03-Oct-00	REDNESS	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CLEANSER 6.78 OZ	LAC0926595			006	09-Oct-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MAR0926686	33	Year(s)	Female Adult	10-Oct-00	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	RHO0927095	58	Year(s)	Female Adult	12-Oct-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	WIL0927962			006	17-Oct-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SPE0928088	55	Year(s)	Female Adult	18-Oct-00	PEELING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	DAV0928251			006	19-Oct-00	REDNESS	US	N	SKIN		
AGE DEFYING SERIES CLEANSER PACKETTE	SUM0928852			006	23-Oct-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MIL0928976			006	24-Oct-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SET0929042			006	24-Oct-00	WELTS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	BRU0929827	61	Year(s)	Female Adult	30-Oct-00	N	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	REG0931513			006	07-Nov-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MOR0931633			006	08-Nov-00	OTHER	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	PER0931907			006	09-Nov-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	HEA0933618	44	Year(s)	Female Adult	21-Nov-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	WEI0933491			006	21-Nov-00	N	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BOL0933743			006	22-Nov-00	FLAKING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	ALD0934222			999	28-Nov-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	ITU0935026	30	Year(s)	Female Adult	04-Dec-00	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	BLA0935216		001	006	05-Dec-00	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	WAT0935066		001	006	05-Dec-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	DEL0935814	54	Year(s)	Female Adult	11-Dec-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SCA0936563	30	Year(s)	Female Adult	15-Dec-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	MCA0936749	29	Year(s)	Female Adult	18-Dec-00	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CLEANSER 6.78 OZ	SHA0937768		001	006	27-Dec-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CLEANSER SZ ND	DE 0937804		001	006	28-Dec-00	REDNESS	US	N	EYE		

COMMENTS FOR OLAY MOISTURIZERS WITH SALICYLIC ACID

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Ctry	MD	Incident	Dur	Amount
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DE 0715898	63	Year(s)	Female Adult	02-Jan-97	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	WEL0715848		Unknown	Unknown	02-Jan-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STA0722731		Unknown	Female Adult	19-Feb-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRE0723346		Unknown	Female Adult	24-Feb-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEA0724563		Unknown	Female Adult	04-Mar-97	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0724539		Unknown	Female Adult	04-Mar-97	RASH	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JON0724670		Unknown	Female Adult	05-Mar-97	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0724796		Unknown	Female Adult	06-Mar-97	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SAN0725042		Unknown	Female Adult	07-Mar-97	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRE0725247		Unknown	Female Adult	10-Mar-97	BLEMISHES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAT0726327	34	Year(s)	Female Adult	17-Mar-97	ACNE	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAM0726485	49	Year(s)	Female Adult	18-Mar-97	REDNESS	US	N	EYE	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	YUS0726925		Unknown	Female Adult	20-Mar-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ASW0727423		Unknown	Female Adult	24-Mar-97	STINGING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0727547		Unknown	Female Adult	25-Mar-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MEN0727927		Unknown	Female Adult	27-Mar-97	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0728218	50	Year(s)	Female Adult	31-Mar-97	DIFFICULTY	US	N	INHALATION	30	002
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KEL0728801		Unknown	Female Adult	03-Apr-97	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PET0728976		Unknown	Female Adult	07-Apr-97	BLURRED VISION	US	N	EYE	9	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DUR0729373	38	Year(s)	Female Adult	08-Apr-97	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	POK0731505		Unknown	Unknown	23-Apr-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAT0731814	41	Year(s)	Female Adult	24-Apr-97	BURNING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0732178	80	Year(s)	Female Adult	28-Apr-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	LEV0732132		Unknown	Male Adult	28-Apr-97	ASTHMA ATTACK	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	ENG0732556	80	Year(s)	Female Adult	30-Apr-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0732452		Unknown	Female Adult	30-Apr-97	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FRY0732730	53	Year(s)	Female Adult	01-May-97	VOMITING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAG0732890		Unknown	Female Adult	02-May-97	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0732841	52	Year(s)	Female Adult	02-May-97	RASH	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	GOL0732941		Unknown	Female Adult	05-May-97	HEADACHE	US	N	INHALATION		
AGE DEFYING SERIES CREAM PACKETTE	KLE0733145		Unknown	Female Adult	05-May-97	BURNING	US	N	EYE		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	SUD0733017		Unknown	Female Adult	05-May-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0733217		Unknown	Female Adult	06-May-97	RASH	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	ZAP0733606		Unknown	Female Adult	12-May-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0733843		Unknown	Female Adult	12-May-97	SNEEZING	US	N	INHALATION		
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	MC 0734087	60	Year(s)	Female Adult	13-May-97	BURNING	US	N	SKIN	3	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	OST0734059		Unknown	Female Adult	13-May-97	IRRITATION	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	COR0734319		Unknown	Female Adult	14-May-97	BURNING	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	PAY0734265	42	Year(s)	Female Adult	14-May-97	REDNESS	US	N	EYE	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	SHA0734376		Unknown	Female Adult	14-May-97	BUMPS	US	N	SKIN	10	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOC0734199		Unknown	Female Adult	14-May-97	STINGING	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0734400	28	Year(s)	Female Adult	14-May-97	SWELLING	US	N	EYE INDIRECT	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0734400	35	Year(s)	Male Adult	14-May-97	SWELLING	US	N	EYE INDIRECT	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0734255	73	Year(s)	Female Adult	14-May-97	INFECTION	US	N	EYE	9	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEV0734447	69	Year(s)	Female Adult	16-May-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	PAR0734457		Unknown	Female Adult	16-May-97	LUMPS	US	N	SKIN	10	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	ERH0734642		Unknown	Female Adult	19-May-97	RASH	US	N	SKIN	3	007
OLAY DAILY RENEWAL CREAM 2 OZ	NEW0734842	28	Year(s)	Female Adult	19-May-97	RASH	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	POD0734883	45	Year(s)	Female Adult	19-May-97	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0734711		Unknown	Female Adult	19-May-97	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TES0734735	46	Year(s)	Female Adult	19-May-97	BURNING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0734904		Unknown	Female Adult	19-May-97	RASH	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	KLI0735112		Unknown	Female Adult	20-May-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PET0735072		Unknown	Female Adult	20-May-97	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRU0735055	23	Year(s)	Female Adult	20-May-97	ACNE	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	ALE0735171		Unknown	Female Adult	21-May-97	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0735179	70	Year(s)	Female Adult	21-May-97	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0735401		Unknown	Female Adult	22-May-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	HIE0735354		Unknown	Female Adult	22-May-97	FLAKING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NON0735768		Unknown	Unknown	27-May-97	BURNING	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	HUB0735879		Unknown	Unknown	27-May-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0735812		Unknown	Female Adult	27-May-97	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OPD0735756		Unknown	Unknown	27-May-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0735754	27	Year(s)	Female Adult	27-May-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TRO0735671		Unknown	Female Adult	27-May-97	BURNING	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	RYM0735937		Unknown	Female Adult	28-May-97	RASH	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	FON0735924		Unknown	Female Adult	28-May-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GUS0735993		Unknown	Female Adult	28-May-97	SNEEZING	US	N	INHALATION		
AGE DEFYING SERIES CREAM PACKETTE	BAT0736190		Unknown	Female Adult	29-May-97	RASH	US	N	SKIN		Unknown
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	LAM0736213	39	Year(s)	Female Adult	29-May-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIT0736101	36	Year(s)	Female Adult	29-May-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	ENG0736287		Unknown	Female Adult	30-May-97	SWELLING	US	Y	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEV0736316		Unknown	Female Adult	30-May-97	HEADACHE	US	N	INHALATION	12	Hour(s)

OLAY DAILY RENEWAL CREAM 2 OZ	MC 0736404		Unknown	Female Adult	30-May-97	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0736614	26	Year(s)	Male Adult	02-Jun-97	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0736462		Unknown	Female Adult	02-Jun-97	BURNING	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	KES0736795		Unknown	Female Adult	03-Jun-97	REDNESS	US	Y	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAN0736751		Unknown	Female Adult	03-Jun-97	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	CLA0736707		Unknown	Female Adult	03-Jun-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0736786		Unknown	Female Adult	03-Jun-97	OTHER	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAL0736782		Unknown	Female Adult	03-Jun-97	HIVES	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	WEI0736679		Unknown	Female Adult	03-Jun-97	BUMPS	US	N	SKIN	3	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	DUL0737026	37	Year(s)	Female Adult	04-Jun-97	DISCOLORATION	US	Y	SKIN	5	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BUR0737200		Unknown	Female Adult	05-Jun-97	HIVES	US	Y	SKIN	6	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	YAK0737157		Unknown	Female Adult	05-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COG0737260	48	Year(s)	Female Adult	06-Jun-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAJ0737257	42	Year(s)	Female Adult	06-Jun-97	ITCHING	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	HIC0737542	49	Unknown	Female Adult	09-Jun-97	BURNING	US	N	SKIN		
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	MCD0737527		Unknown	Female Adult	09-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0737490		Unknown	Female Adult	09-Jun-97	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOU0737630		Unknown	Female Adult	10-Jun-97	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAR0737586		Unknown	Female Adult	10-Jun-97	BUMPS	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	MON0737921	22	Year(s)	Female Adult	11-Jun-97	BUMPS	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	REF0737893		Unknown	Female Adult	11-Jun-97	STINGING	US	N	SKIN		002
OLAY DAILY RENEWAL CREAM 2 OZ	COL0737936		Unknown	Female Adult	11-Jun-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	VAL0737946	28	Year(s)	Female Adult	11-Jun-97	BURNING	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	ROU0738138	32	Year(s)	Unknown	12-Jun-97	ITCHING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUT0738134	60	Year(s)	Female Adult	12-Jun-97	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0738029		Unknown	Female Adult	12-Jun-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AGD0738318		Unknown	Female Adult	13-Jun-97	ITCHING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEL0738238		Unknown	Female Adult	13-Jun-97	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEL0738400		Unknown	Female Adult	16-Jun-97	REDNESS	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0738597	73	Year(s)	Female Adult	17-Jun-97	CHAPPED	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRO0738603		Unknown	Female Adult	17-Jun-97	ROUGH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAY0738642	53	Year(s)	Female Adult	17-Jun-97	HIVES	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RAT0738672		Unknown	Female Adult	17-Jun-97	BLISTERS	US	N	SKIN	1	007
AGE DEFYING SERIES CREAM PACKETTE	LEV0738911	50	Year(s)	Female Adult	18-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAT0738924	42	Year(s)	Female Adult	18-Jun-97	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOF0739066		Unknown	Female Adult	19-Jun-97	WRINKLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0738963	79	Year(s)	Female Adult	19-Jun-97	IRRITATION	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JON0739170	74	Year(s)	Female Adult	20-Jun-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HER0739168		Unknown	Female Adult	20-Jun-97	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	VIL0739158		Unknown	Male Adult	20-Jun-97	REDNESS	US	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0739457		Unknown	Female Adult	23-Jun-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOL0739745	53	Year(s)	Female Adult	24-Jun-97	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0739749	62	Year(s)	Female Adult	24-Jun-97	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LIN0739612		Unknown	Female Adult	24-Jun-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0739796		Unknown	Unknown	25-Jun-97	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MUR0739920		Unknown	Female Adult	25-Jun-97	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAT0739941		Unknown	Female Adult	26-Jun-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOR0739964		Unknown	Female Adult	26-Jun-97	IRRITATION	US	N	EYE INDIRECT	14	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0740039	54	Year(s)	Female Adult	26-Jun-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEG0739963		Unknown	Female Adult	26-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WEB0740101	75	Year(s)	Female Adult	26-Jun-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0740491		Unknown	Female Adult	30-Jun-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0740500	44	Year(s)	Female Adult	30-Jun-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0740367		Unknown	Female Adult	30-Jun-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUM0740837	69	Year(s)	Female Adult	02-Jul-97	REDNESS	US	N	SKIN	5	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ILL0741021		Unknown	Female Adult	03-Jul-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0741330	50	Year(s)	Female Adult	07-Jul-97	IRRITATION	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POW0741385	42	Year(s)	Female Adult	07-Jul-97	ITCHING	US	N	EYE INDIRECT	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0741389		Unknown	Female Adult	07-Jul-97	CHOKING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0741404		Unknown	Female Adult	08-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DUN0741654		Unknown	Female Adult	09-Jul-97	DRYNESS	US	N	SKIN	2	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FEL0741726		Unknown	Female Adult	09-Jul-97	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MCD0741667	74	Year(s)	Unknown	09-Jul-97	RASH	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0741854		Unknown	Female Adult	10-Jul-97	SUNBURN	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEZ0741807		Unknown	Female Adult	10-Jul-97	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	WRI0741952		Unknown	Female Adult	10-Jul-97	RASH	US	Y	SKIN	4	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	WYN0742348	50	Year(s)	Female Adult	14-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	THO0742726		Unknown	Female Adult	16-Jul-97	WELTS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VIE0742659		Unknown	Female Adult	16-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	REI0742766		Unknown	Female Adult	17-Jul-97	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RUR0742765		Unknown	Female Adult	17-Jul-97	TEARING	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0743031		Unknown	Female Adult	18-Jul-97	STINGING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	COS0743000		Unknown	Female Adult	18-Jul-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIS0742942		Unknown	Unknown	18-Jul-97	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	LAN0742953		Unknown	Unknown	18-Jul-97	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0743146	40	Year(s)	Female Adult	21-Jul-97	ACNE	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JES0743520	69	Year(s)	Female Adult	22-Jul-97	ROUGH	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	RHO0743510		Unknown	Female Adult	22-Jul-97	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	SHO0743358	49	Year(s)	Female Adult	22-Jul-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0743867		Unknown	Female Adult	24-Jul-97	BUMPS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0743877		Unknown	Unknown	24-Jul-97	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	YAN0743888		Unknown	Female Adult	25-Jul-97	ROUGH	US	N	SKIN	5	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BAU0744426		Unknown	Female Adult	29-Jul-97	HEADACHE	US	N	INHALATION	10	002
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0744398		Unknown	Female Adult	29-Jul-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NEW0744538		Unknown	Unknown	29-Jul-97	PEELING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TOS0744414		Unknown	Female Adult	29-Jul-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	WAL0744411		Unknown	Female Adult	29-Jul-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0744727		Unknown	Unknown	30-Jul-97	DRYNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GEM0744768		Unknown	Female Adult	31-Jul-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0744957		Unknown	Female Adult	01-Aug-97	FLAKING	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0745025		Unknown	Female Adult	01-Aug-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SAD0745140	44	Year(s)	Female Adult	04-Aug-97	SORES	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	SNO0745579		Unknown	Female Adult	05-Aug-97	IRRITATION	US	N	EYE	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0745408		Unknown	Unknown	05-Aug-97	BLEMISHES	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEN0745815	54	Year(s)	Female Adult	07-Aug-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0745972		Unknown	Female Adult	08-Aug-97	REDNESS	US	Y	SKIN	1	Week(s)
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	CHA0746282		Unknown	Female Adult	11-Aug-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAD0746144		Unknown	Female Adult	11-Aug-97	BURNING	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	SCU0746575	71	Year(s)	Female Adult	12-Aug-97	BURNING	US	Y	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0746443		Unknown	Female Adult	12-Aug-97	BUMPS	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCU0746739	71	Year(s)	Female Adult	13-Aug-97	REDNESS	US	N	EYE	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0746836		Unknown	Female Adult	14-Aug-97	DRYNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	HOU0747032	54	Year(s)	Female Adult	15-Aug-97	TIGHTNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAT0747114		Unknown	Female Adult	15-Aug-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BEC0747332		Unknown	Female Adult	18-Aug-97	HEADACHE	US	N	ORAL/NASAL		
OLAY DAILY RENEWAL CREAM 2 OZ	COS0747217		Unknown	Female Adult	18-Aug-97	CUT	US	N	INJURY	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOW0747288	68	Year(s)	Female Adult	18-Aug-97	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PLU0747381		Unknown	Female Adult	18-Aug-97	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	UNK0747414	48	Year(s)	Female Adult	18-Aug-97	ACNE	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0747854		Unknown	Female Adult	20-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEA0748096		Unknown	Female Adult	22-Aug-97	BLISTERS	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	BOA0748269	33	Year(s)	Female Adult	22-Aug-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BYR0748112		Unknown	Female Adult	22-Aug-97	SORES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CRE0748399		Unknown	Female Adult	25-Aug-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TRI0748371		Unknown	Female Adult	25-Aug-97	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DYS0748769	48	Year(s)	Female Adult	26-Aug-97	PEELING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ZOM0748868		Unknown	Female Adult	27-Aug-97	DISCOLORATION	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0749015		Unknown	Female Adult	28-Aug-97	BLISTERS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0749250		Unknown	Female Adult	29-Aug-97	DISCOLORATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STE0749245		Unknown	Unknown	29-Aug-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GUI0749411		Unknown	Female Adult	02-Sep-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SPI0749362		Unknown	Female Adult	02-Sep-97	REDNESS	US	N	EYE	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAS0749685	45	Year(s)	Female Adult	03-Sep-97	PIMPLES	US	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAL0749732		Unknown	Female Adult	03-Sep-97	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAA0749736	28	Year(s)	Female Adult	03-Sep-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0749928		Unknown	Female Adult	04-Sep-97	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAD0750213		Unknown	Female Adult	05-Sep-97	RASH	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUS0750481	46	Year(s)	Female Adult	08-Sep-97	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HIG0750408		Unknown	Female Adult	08-Sep-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0750437		Unknown	Female Adult	08-Sep-97	SORENESS	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0750362		Unknown	Female Adult	08-Sep-97	DRYNESS	US	Y	SKIN	6	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JON0750870	32	Year(s)	Female Adult	10-Sep-97	ACNE	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0750842	65	Year(s)	Female Adult	10-Sep-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COU0751055		Unknown	Female Adult	11-Sep-97	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEM0751247		Unknown	Female Adult	12-Sep-97	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LIV0751363	71	Year(s)	Female Adult	12-Sep-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CEC0751439		Unknown	Female Adult	15-Sep-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0751663	34	Year(s)	Female Adult	15-Sep-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0751510		Unknown	Female Adult	15-Sep-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0751639		Unknown	Female Adult	15-Sep-97	REDNESS	US	N	EYE	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0751724		Unknown	Female Adult	16-Sep-97	RASH	US	N	SKIN		Hour(s)
OLAY DAILY RENEWAL LOTION 4 OZ	TAN0751894		Unknown	Female Adult	16-Sep-97	RASH	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	LIM0752067		Unknown	Unknown	17-Sep-97	SNEEZING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	PAN0752094	22	Year(s)	Female Adult	17-Sep-97	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SAN0752043		Unknown	Female Adult	17-Sep-97	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WEI0752114		Unknown	Unknown	17-Sep-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POP0752235		Unknown	Female Adult	18-Sep-97	BURNING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEI0752563		Unknown	Unknown	19-Sep-97	ACNE	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	EHL0752553		Unknown	Female Adult	19-Sep-97	SWELLING	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0752461		Unknown	Female Adult	19-Sep-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	THO0752488		Unknown	Female Adult	19-Sep-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	YOU0752434	40	Year(s)	Female Adult	19-Sep-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	CAS0752890		Unknown	Female Adult	22-Sep-97	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAN0752773		Unknown	Female Adult	22-Sep-97	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	INT0752963		Unknown	Female Adult	22-Sep-97	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0752882	60	Year(s)	Female Adult	22-Sep-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NEI0752853	44	Year(s)	Female Adult	22-Sep-97	SWELLING	US	N	SKIN	8	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARN0753008		Unknown	Female Adult	23-Sep-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0753170		Unknown	Female Adult	23-Sep-97	WELTS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEN0753261		Unknown	Female Adult	24-Sep-97	BUMPS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUS0753299	46	Year(s)	Female Adult	24-Sep-97	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0753241		Unknown	Female Adult	24-Sep-97	BURNING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAL0753304		Unknown	Female Adult	24-Sep-97	REDNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DUR0753496		Unknown	Female Adult	25-Sep-97	TINGLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOR0753753	60	Year(s)	Female Adult	26-Sep-97	BUMPS	US	N	SKIN	1.5	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COR0753916		Unknown	Female Adult	29-Sep-97	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LIN0754079	53	Year(s)	Female Adult	29-Sep-97	REDNESS	US	N	EYE INDIRECT	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEY0753937		Unknown	Unknown	29-Sep-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEY0753937		Unknown	Unknown	29-Sep-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAL0754151		Unknown	Female Adult	30-Sep-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAL0754151		Unknown	Female Adult	30-Sep-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRY0754223		Unknown	Female Adult	30-Sep-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRY0754223		Unknown	Female Adult	30-Sep-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0754147		Unknown	Female Adult	30-Sep-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0754147		Unknown	Female Adult	30-Sep-97	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0754499		Unknown	Female Adult	01-Oct-97	DRYNESS	US	N	SKIN	8	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0754499		Unknown	Female Adult	01-Oct-97	DRYNESS	US	N	SKIN	8	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0754405		Unknown	Female Adult	01-Oct-97	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0754405		Unknown	Female Adult	01-Oct-97	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAW0754398	3	Year(s)	004	01-Oct-97	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	PAW0754398	3	Year(s)	004	01-Oct-97	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	ROC0754435	40	Year(s)	Female Adult	01-Oct-97	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROC0754435	40	Year(s)	Female Adult	01-Oct-97	PIMPLES	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROT0754575		Unknown	Female Adult	02-Oct-97	DRYNESS	US	N	SKIN	12	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROT0754575		Unknown	Female Adult	02-Oct-97	DRYNESS	US	N	SKIN	12	Day(s)

AGE DEFYING SERIES CREAM PACKETTE	UNK0755038		Unknown	Unknown	06-Oct-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0754999		Unknown	Female Adult	06-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0754999		Unknown	Female Adult	06-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TER0755047	28	Year(s)	Female Adult	06-Oct-97	BLISTERS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0755047	28	Year(s)	Female Adult	06-Oct-97	BLISTERS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIE0755003		Unknown	Female Adult	06-Oct-97	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	WIE0755003		Unknown	Female Adult	06-Oct-97	REDNESS	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	BAD0755689		Unknown	Female Adult	08-Oct-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAD0755689		Unknown	Female Adult	08-Oct-97	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LUE0755758		Unknown	Female Adult	08-Oct-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LUE0755758		Unknown	Female Adult	08-Oct-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ING0755922	34	Year(s)	Female Adult	09-Oct-97	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ING0755922	34	Year(s)	Female Adult	09-Oct-97	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAM0755951		Unknown	Unknown	09-Oct-97	ITCHING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAM0755951		Unknown	Unknown	09-Oct-97	ITCHING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EDG0756203		Unknown	Female Adult	10-Oct-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EDG0756203		Unknown	Female Adult	10-Oct-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0756166	54	Year(s)	Female Adult	10-Oct-97	PEELING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0756166	54	Year(s)	Female Adult	10-Oct-97	PEELING	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LOC0756561		Unknown	Male Adult	14-Oct-97	RASH	US	N	SKIN	3	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LOC0756561		Unknown	Male Adult	14-Oct-97	RASH	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0756713		Unknown	Female Adult	14-Oct-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0756713		Unknown	Female Adult	14-Oct-97	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SUN0756878	45	Year(s)	Female Adult	15-Oct-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUN0756878	45	Year(s)	Female Adult	15-Oct-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WES0756828		Unknown	Female Adult	15-Oct-97	OTHER	US	Y	EYE	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WES0756828		Unknown	Female Adult	15-Oct-97	OTHER	US	Y	EYE	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	HEN0757039	62	Year(s)	Female Adult	16-Oct-97	STINGING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EAR0757197		Unknown	Unknown	16-Oct-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MUE0757193		Unknown	Female Adult	16-Oct-97	RASH	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	FRE0757481		Unknown	Female Adult	17-Oct-97	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	WAT0757297	111	Unknown	Female Adult	17-Oct-97	TEARING	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KUG0757535		Unknown	Female Adult	20-Oct-97	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0757857		Unknown	Female Adult	21-Oct-97	RUNNY NOSE	US	N	INHALATION	1	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROM0757995		Unknown	Female Adult	21-Oct-97	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0758181	28	Year(s)	Female Adult	22-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STR0758424		Unknown	Female Adult	23-Oct-97	RASH	US	N	SKIN	4	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	XIE0758417		Unknown	Female Adult	23-Oct-97	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL LOTION 4 OZ	CRO0758395		Unknown	Unknown	23-Oct-97	RASH	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAH0758651		Unknown	Female Adult	24-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BOC0758794		Unknown	Female Adult	27-Oct-97	BURNING	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0758969		Unknown	Female Adult	27-Oct-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOF0758936	42	Unknown	Female Adult	27-Oct-97	RASH	CA	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	COL0759119			Female Adult	28-Oct-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0759217	64	Year(s)	Female Adult	28-Oct-97	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DES0759395		Unknown	Female Adult	29-Oct-97	DRYNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAL0759510		Unknown	Unknown	29-Oct-97	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	POO0759391		Unknown	Female Adult	29-Oct-97	DIFFICULTY	US	N	INHALATION		
AGE DEFYING SERIES CREAM PACKETTE	SWA0759585		Unknown	Female Adult	30-Oct-97	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUL0759603		Unknown	Unknown	30-Oct-97	ROUGH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0760040		Unknown	Female Adult	03-Nov-97	PIMPLES	US	N	SKIN	5	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	O^N0760394	42	Year(s)	Female Adult	04-Nov-97	WELTS	US	N	SKIN	2.5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0760313		Unknown	Female Adult	04-Nov-97	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HOO0760409	46	Year(s)	Female Adult	04-Nov-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RUH0760663		Unknown	Female Adult	05-Nov-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ZOE0760838		Unknown	Female Adult	06-Nov-97	ITCHING	US	N	SKIN	5	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	CLA0761032	55	Year(s)	Female Adult	07-Nov-97	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUC0761000		Unknown	Female Adult	07-Nov-97	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOM0761194	40	Year(s)	Female Adult	07-Nov-97	BURNING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	LEO0761044		Unknown	Female Adult	07-Nov-97	DRYNESS	US	N	SKIN		Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCH0761489	48	Year(s)	Female Adult	10-Nov-97	BUMPS	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0761369		Unknown	Female Adult	10-Nov-97	TEARING	US	N	EYE INDIRECT	6	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COI0761609		Unknown	Female Adult	11-Nov-97	BURNING	US	N	SKIN	14	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOL0761659		Unknown	Unknown	11-Nov-97	BLURRED VISION	US	N	EYE	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRE0761646		Unknown	Female Adult	11-Nov-97	SWELLING	US	N	SKIN	4	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOC0761732		Unknown	Female Adult	11-Nov-97	REDNESS	US	N	EYE	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAR0761639		Unknown	Female Adult	11-Nov-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SWI0761677		Unknown	Female Adult	11-Nov-97	BUMPS	US	N	SKIN		Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MOO0761968	35	Year(s)	Female Adult	12-Nov-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0761989	68	Year(s)	Female Adult	12-Nov-97	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEA0762207		Unknown	Female Adult	13-Nov-97	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAS0762458		Unknown	Female Adult	14-Nov-97	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SPA0762348		Unknown	Female Adult	14-Nov-97	DRYNESS	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KEL0762737	30	Year(s)	Female Adult	17-Nov-97	STINGING	US	N	SKIN	5	002

OLAY DAILY RENEWAL CREAM 2 OZ	BIC0762566		Unknown	Female Adult	17-Nov-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEN0762660		Unknown	Female Adult	17-Nov-97	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIC0762706	44	Year(s)	Female Adult	17-Nov-97	HIVES	CA	N	SKIN	6	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RAM0762863	36	Year(s)	Female Adult	17-Nov-97	RASH	US	N	SKIN	1.5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RAN0762544		Unknown	Female Adult	17-Nov-97	SWELLING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PRY0763059	48	Year(s)	Female Adult	18-Nov-97	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0762874		Unknown	Female Adult	18-Nov-97	ITCHING	US	N	EYE	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0763410	47	Year(s)	Female Adult	19-Nov-97	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FIE0763309		Unknown	Female Adult	19-Nov-97	REDNESS	US	N	SKIN	4	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0763286		Unknown	Unknown	19-Nov-97	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MYR0763341	29	Year(s)	Female Adult	19-Nov-97	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUC0763562		Unknown	Unknown	20-Nov-97	BURNING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GUT0763659		Unknown	Female Adult	21-Nov-97	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0763874		Unknown	Male Adult	21-Nov-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SER0763696		Unknown	Unknown	21-Nov-97	RAW	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALI0764049		Unknown	Female Adult	24-Nov-97	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CIN0764016	33	Year(s)	Female Adult	24-Nov-97	ITCHING	CA	N	SKIN	6	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CRA0764082		Unknown	Female Adult	24-Nov-97	BLISTERS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRE0764236		Unknown	Female Adult	24-Nov-97	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0764239		Unknown	Female Adult	24-Nov-97	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PUT0764363		Unknown	Female Adult	25-Nov-97	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STE0764411	22	Year(s)	Female Adult	25-Nov-97	REDNESS	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BUR0764618		Unknown	Female Adult	26-Nov-97	RAW	US	N	SKIN		Hour(s)
AGE DEFYING SERIES CREAM PACKETTE	SMA0764633		Unknown	Female Adult	26-Nov-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SUN0764652		Unknown	Female Adult	26-Nov-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0765208		Unknown	Female Adult	02-Dec-97	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRA0765189		Unknown	Female Adult	02-Dec-97	SORES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0765250		Unknown	Unknown	02-Dec-97	FLAKING	US	N	SKIN	2	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	ATK0765641	38	Year(s)	Female Adult	03-Dec-97	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0765446	26	Year(s)	Female Adult	03-Dec-97	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0765521		Year(s)	Female Adult	03-Dec-97	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAD0765629	21	Year(s)	Female Adult	03-Dec-97	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOM0765735		Unknown	Unknown	04-Dec-97	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARL0766066	32	Year(s)	Female Adult	05-Dec-97	ACNE	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRE0766010	37	Year(s)	Female Adult	05-Dec-97	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GAR0766235		Unknown	Female Adult	08-Dec-97	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHA0766336		Unknown	Unknown	08-Dec-97	PEELING	US	Y	SKIN	3	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUR0766868		Unknown	Female Adult	11-Dec-97	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0767073		Unknown	Female Adult	11-Dec-97	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAL0767186	51	Year(s)	Female Adult	12-Dec-97	BUMPS	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIC0767087	43	Year(s)	Female Adult	12-Dec-97	BUMPS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0767176		Unknown	Female Adult	12-Dec-97	HIVES	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	LAU0767532	41	Year(s)	Female Adult	15-Dec-97	WELTS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAU0767445		Unknown	Female Adult	15-Dec-97	ROUGH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LON0767399		Unknown	Female Adult	15-Dec-97	PEELING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	LAW0767748		Unknown	Female Adult	16-Dec-97	IRRITATION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	BAI0767955		Unknown	Female Adult	17-Dec-97	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FAS0768001	30	Year(s)	Female Adult	17-Dec-97	RASH	CA	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	POO0768227	48	Year(s)	Female Adult	18-Dec-97	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0768364		Unknown	Unknown	19-Dec-97	RY/AGITATED	US	N	SKIN	30	002
OLAY DAILY RENEWAL CREAM 2 OZ	PRI0768317	79	Year(s)	Female Adult	19-Dec-97	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0768639		Unknown	Female Adult	22-Dec-97	REDNESS	US	N	EYE INDIRECT		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0768543		Unknown	Female Adult	22-Dec-97	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOO0768761		Unknown	Unknown	23-Dec-97	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RED0769054		Unknown	Female Adult	29-Dec-97	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0768917	60	Year(s)	Female Adult	29-Dec-97	BAD TASTE IN MOUTH	US	N	ORAL/NASAL		
OLAY DAILY RENEWAL CREAM 2 OZ	FEL0769632	50	Year(s)	Female Adult	31-Dec-97	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0769516	42	Year(s)	Female Adult	31-Dec-97	BUMPS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIB0769583	33	Year(s)	Female Adult	31-Dec-97	BURNING	CA	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DYE0769865		Unknown	Unknown	02-Jan-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0769874	66	Year(s)	Female Adult	02-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LAB0770016		Unknown	Female Adult	05-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOM0770089	53	Year(s)	Female Adult	05-Jan-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MEE0770379		Unknown	Female Adult	06-Jan-98	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VLA0770403		Unknown	Female Adult	06-Jan-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARC0770640		Unknown	Female Adult	07-Jan-98	OTHER	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BLU0770827		Unknown	Female Adult	07-Jan-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0770697		Unknown	Female Adult	07-Jan-98	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0770882	37	Year(s)	Female Adult	07-Jan-98	STINGING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	LOT0770957		Unknown	Female Adult	08-Jan-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAB0771119		Unknown	Female Adult	09-Jan-98	BURNING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAB0771120	33	Year(s)	Unknown	09-Jan-98	BURNING	US	N	EYE INDIRECT	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0771162		Unknown	Female Adult	09-Jan-98	TEARING	US	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SIN0771110		Unknown	Female Adult	09-Jan-98	SWELLING	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	HOR0771502		Unknown	Unknown	12-Jan-98	STINGING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LET0771696		Unknown	Female Adult	13-Jan-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	DAY0771936		Unknown	Unknown	14-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DYS0771934	75	Year(s)	Female Adult	14-Jan-98	PIMPLES	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FIR0772131	54	Year(s)	Female Adult	14-Jan-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0771927	39	Year(s)	Female Adult	14-Jan-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0772274		Unknown	Female Adult	15-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DEL0772464		Unknown	Female Adult	16-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TOD0772473	45	Year(s)	Female Adult	16-Jan-98	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ROV0772697		Unknown	Female Adult	20-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAM0773026	34	Year(s)	Female Adult	21-Jan-98	DRYNESS	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ZOU0773092	45	Year(s)	Female Adult	21-Jan-98	BURNING	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WEM0773417		Unknown	Female Adult	22-Jan-98	WELTS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DEV0773539		Unknown	Female Adult	23-Jan-98	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0773522		Unknown	Female Adult	23-Jan-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HEM0773612	31	Year(s)	Female Adult	23-Jan-98	BLEEDING	US	Y	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DRU0774051		Unknown	Unknown	27-Jan-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIR0774098		Unknown	Female Adult	27-Jan-98	REDNESS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LIN0774194		Unknown	Female Adult	27-Jan-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	YAS0774192		Unknown	Female Adult	27-Jan-98	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REF0774359		Unknown	Female Adult	28-Jan-98	REDNESS	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRE0774513		Unknown	Female Adult	28-Jan-98	DRYNESS	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BLE0774666	49	Year(s)	Unknown	29-Jan-98	SWELLING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHR0774834	42	Year(s)	Female Adult	29-Jan-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0774785		Unknown	Female Adult	29-Jan-98	DRYNESS	US	Y	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LIP0774786		Unknown	Female Adult	29-Jan-98	ITCHING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STA0774867	33	Year(s)	Female Adult	29-Jan-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DEV0774925		Unknown	Unknown	30-Jan-98	ACNE	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0775131		Unknown	Female Adult	02-Feb-98	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0775096	40	Year(s)	Female Adult	02-Feb-98	RASH	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	MUN0775289		Unknown	Female Adult	02-Feb-98	BLURRED VISION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0775455	37	Year(s)	Female Adult	03-Feb-98	REDNESS	US	N	SKIN	4	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0775495		Unknown	Female Adult	03-Feb-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OVE0775726		Unknown	Unknown	04-Feb-98	REDNESS	US	Y	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	JAN0775887		Unknown	Female Adult	05-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KAL0775897		Unknown	Female Adult	05-Feb-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RHO0775965		Unknown	Female Adult	05-Feb-98	RAW	US	N	SKIN	5	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	WAL0776253		Unknown	Male Adult	06-Feb-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0776506	59	Year(s)	Female Adult	09-Feb-98	ACNE	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DIA0776507	29	Unknown	Female Adult	09-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MCN0776391		Unknown	Female Adult	09-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PER0776434	38	Year(s)	Female Adult	09-Feb-98	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAS0776446		Unknown	Female Adult	09-Feb-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAS0776577		Unknown	Female Adult	09-Feb-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LIP0777097		Unknown	Female Adult	11-Feb-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ROZ0776944	35	Year(s)	Female Adult	11-Feb-98	SWELLING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FYF0777194		Unknown	Female Adult	12-Feb-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOS0777377	27	Year(s)	Female Adult	12-Feb-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0777266		Unknown	Female Adult	12-Feb-98	CHAPPED	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ABI0777441		Unknown	Unknown	13-Feb-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0777520		Unknown	Female Adult	13-Feb-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	(RE0777580		Unknown	Unknown	16-Feb-98	CRACKING	CA	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	SAL0777858		Unknown	Female Adult	17-Feb-98	RASH	US	N	SKIN		Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GRO0777690		Unknown	Unknown	17-Feb-98	BUMPS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	MIE0777772		Unknown	Female Adult	17-Feb-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0777803	70	Year(s)	Female Adult	17-Feb-98	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHE0777951		Unknown	Female Adult	18-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MER0778174	39	Year(s)	Female Adult	18-Feb-98	STINGING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TIL0777997	45	Year(s)	Female Adult	18-Feb-98	RASH	CA	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRE0778095		Unknown	Female Adult	18-Feb-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOS0778176	39	Year(s)	Female Adult	18-Feb-98	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOB0778417	57	Year(s)	Female Adult	19-Feb-98	PIMPLES	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MUN0778288	38	Year(s)	Female Adult	19-Feb-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STE0778341		Unknown	Female Adult	19-Feb-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ANK0778646		Unknown	Male Adult	20-Feb-98	RASH	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAK0778554	45	Year(s)	Female Adult	20-Feb-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAM0778613	48	Year(s)	Female Adult	20-Feb-98	RASH	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MUL0778766	48	Year(s)	Female Adult	23-Feb-98	SWELLING	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0779029		Unknown	Female Adult	24-Feb-98	SCRATCH	US	N	SKIN	2	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STE0779318		Unknown	Female Adult	25-Feb-98	PIMPLES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0779333	38	Year(s)	Female Adult	25-Feb-98	SWELLING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUT0779375	65	Year(s)	Female Adult	25-Feb-98	PEELING	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	COL0779510		Unknown	Unknown	26-Feb-98	RASH	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HIC0779492		Unknown	Female Adult	26-Feb-98	BUMPS	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0779786		Unknown	Female Adult	27-Feb-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALF0779801		Unknown	Female Adult	27-Feb-98	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GON0779854		Unknown	Female Adult	27-Feb-98	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0780039		Unknown	Female Adult	02-Mar-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAC0779994		Unknown	Female Adult	02-Mar-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAU0780229		Unknown	Female Adult	02-Mar-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FOW0780340	44	Year(s)	Female Adult	03-Mar-98	SWELLING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JAN0780310		Unknown	Unknown	03-Mar-98	REDNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOS0780628	35	Year(s)	Female Adult	04-Mar-98	HIVES	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAD0780575		Unknown	Female Adult	04-Mar-98	SNEEZING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HEN0780527	58	Year(s)	Female Adult	04-Mar-98	HIVES	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REF0780725		Unknown	Female Adult	04-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEL0780538	72	Year(s)	Female Adult	04-Mar-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SOR0780771	37	Year(s)	Male Adult	04-Mar-98	BLISTERS	US	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0780656		Unknown	Unknown	04-Mar-98	RASH	US	N	SKIN	5	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0780814		Unknown	Female Adult	05-Mar-98	CRACKING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KLA0780808		Unknown	Female Adult	05-Mar-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAZ0780787		Unknown	Female Adult	05-Mar-98	PIMPLES	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAY0780863	50	Year(s)	Female Adult	05-Mar-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SOM0780920	70	Year(s)	Female Adult	05-Mar-98	TEARING	CA	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TIL0780903	48	Year(s)	Female Adult	05-Mar-98	HIVES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DUR0781080	61	Year(s)	Female Adult	06-Mar-98	HIVES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SPE0781097		Unknown	Female Adult	06-Mar-98	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0781553	46	Year(s)	Female Adult	09-Mar-98	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0781439		Unknown	Female Adult	09-Mar-98	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0781528		Unknown	Female Adult	09-Mar-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOF0781527		Unknown	Female Adult	09-Mar-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WOO0781447		Unknown	Female Adult	09-Mar-98	HIVES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GUA0781768	59	Year(s)	Female Adult	10-Mar-98	ROUGH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MEA0781607		Unknown	Female Adult	10-Mar-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIS0781698		Unknown	Female Adult	10-Mar-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WID0781752		Unknown	Unknown	10-Mar-98	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOR0781716		Unknown	Female Adult	10-Mar-98	REDNESS	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JON0781978	73	Year(s)	Female Adult	11-Mar-98	(GENERALIZED)	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALV0782065		Unknown	Female Adult	11-Mar-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0782041		Unknown	Female Adult	11-Mar-98	IRRITATION	US	N	SKIN		Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAB0782197		Unknown	Female Adult	12-Mar-98	RASH	US	N	SKIN	1	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	BUR0782212		Unknown	Female Adult	12-Mar-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0782298	34	Unknown	Female Adult	12-Mar-98	ACNE	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COO0782254		Unknown	Female Adult	12-Mar-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0782357	36	Year(s)	Female Adult	12-Mar-98	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JAH0782153		Unknown	Male Adult	12-Mar-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0782278	70	Year(s)	Female Adult	12-Mar-98	CRACKING	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	WIN0782349		Unknown	Female Adult	12-Mar-98	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOO0782216		Unknown	Female Adult	12-Mar-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COL0782574		Unknown	Female Adult	13-Mar-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EVA0782474		Unknown	Female Adult	13-Mar-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAU0782437		Unknown	Female Adult	13-Mar-98	DIFFICULTY	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	FUR0782682		Unknown	Female Adult	16-Mar-98	REDNESS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAD0782775	61	Year(s)	Female Adult	16-Mar-98	SWELLING	CA	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAU0782684		Unknown	Unknown	16-Mar-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JIT0783012	36	Year(s)	Male Adult	16-Mar-98	RASH	US	Y	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RES0782761		Unknown	Female Adult	16-Mar-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARN0783156		Unknown	Unknown	17-Mar-98	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAT0783026		Unknown	Female Adult	17-Mar-98	ACNE	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEM0783152	63	Unknown	Female Adult	17-Mar-98	TEARING	US	N	EYE INDIRECT	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAN0783177	35	Year(s)	Female Adult	17-Mar-98	RASH	CA	N	SKIN	15	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUS0783302	46	Year(s)	Male Adult	17-Mar-98	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL LOTION 4 OZ	FRA0783250	30	Year(s)	Female Adult	17-Mar-98	SWELLING	US	N	SKIN	15	002
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0783340		Unknown	Female Adult	18-Mar-98	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PLA0783368	35	Year(s)	Female Adult	18-Mar-98	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	IAF0783860	45	Year(s)	Female Adult	20-Mar-98	DISCOLORATION	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OST0784027	37	Year(s)	Male Adult	20-Mar-98	RASH	US	Y	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0783838		Unknown	Female Adult	20-Mar-98	REDNESS	US	Y	EYE	1	Months(s)
AGE DEFYING SERIES CREAM PACKETTE	BRE0784143		Unknown	Female Adult	23-Mar-98	SWELLING	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	HUD0784154	57	Year(s)	Female Adult	23-Mar-98	BLURRED VISION	US	N	EYE INDIRECT	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	MIT0784114	68	Year(s)	Female Adult	23-Mar-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAY0784215	79	Year(s)	Female Adult	23-Mar-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DHA0784390	44	Year(s)	Female Adult	23-Mar-98	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VAL0784346		Unknown	Female Adult	23-Mar-98	RASH	US	N	SKIN	3	Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	BAI0784549		Unknown	Female Adult	24-Mar-98	TIGHTNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0784478		Unknown	Unknown	24-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LOS0784609	47	Year(s)	Male Adult	24-Mar-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0784589		Unknown	Female Adult	24-Mar-98	REDNESS	US	Y	SKIN	10	Day(s)

OLAY DAILY RENEWAL LOTION 4 OZ	OSB0784492		Unknown	Female Adult	24-Mar-98	RASH	US	N	SKIN	12	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	SCH0784588		Unknown	Female Adult	24-Mar-98	CRACKING	US	Y	SKIN	10	Unknown
AGE DEFYING SERIES CREAM PACKETTE	LEE0784901		Unknown	Female Adult	25-Mar-98	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	COA0784804	29	Year(s)	Female Adult	25-Mar-98	SWELLING	CA	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIN0784787	26	Year(s)	Female Adult	25-Mar-98	REDNESS	US	N	SKIN	7	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOL0784928		Unknown	Female Adult	26-Mar-98	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0784998		Unknown	Female Adult	26-Mar-98	BURNING	US	N	EYE		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	LOP0784947	40	Year(s)	Female Adult	26-Mar-98	DRYNESS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0784917		Unknown	Female Adult	26-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0785010		Unknown	Female Adult	26-Mar-98	HEADACHE	US	N	INHALATION	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRO0785151	50	Year(s)	Female Adult	27-Mar-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0785426		Unknown	Female Adult	30-Mar-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0785422		Unknown	Female Adult	30-Mar-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0785383	76	Year(s)	Female Adult	30-Mar-98	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSP0785658		Unknown	Male Adult	30-Mar-98	BLISTERS	US	Y	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JER0785674		Unknown	Female Adult	31-Mar-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JON0785694		Unknown	Female Adult	31-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LOS0786076		Unknown	Male Adult	01-Apr-98	BLISTERS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0786006		Unknown	Female Adult	01-Apr-98	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CON0786233		Unknown	Female Adult	02-Apr-98	REDNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VOC0786253	46	Year(s)	Female Adult	02-Apr-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0786374		Unknown	Female Adult	03-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SWA0786438	52	Year(s)	Female Adult	03-Apr-98	SWELLING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEL0786843	25	Year(s)	Female Adult	06-Apr-98	REDNESS	US	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ELL0786645	39	Year(s)	Female Adult	06-Apr-98	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0786679	19	Year(s)	004	06-Apr-98	BUMPS	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	LIS0787033	68	Year(s)	Female Adult	07-Apr-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COS0787103	42	Year(s)	Female Adult	07-Apr-98	SCRATCH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAL0786904	54	Year(s)	Female Adult	07-Apr-98	BUMPS	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	SAL0787140		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	3	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	YOU0787219		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0787290		Unknown	Female Adult	08-Apr-98	RASH	US	N	SKIN	8	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0787184	56	Year(s)	Female Adult	08-Apr-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DUP0787542		Unknown	Female Adult	09-Apr-98	RASH	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	YER0787589		Unknown	Female Adult	09-Apr-98	HEADACHE	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JON0787888	26	Year(s)	Male Adult	13-Apr-98	DIARRHEA	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	POR0787980		Unknown	Unknown	13-Apr-98	REDNESS	US	Y	SKIN	3	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	BEN0788128		Unknown	Female Adult	14-Apr-98	BUMPS	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOU0788258		Unknown	Female Adult	14-Apr-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NOR0788288	33	Year(s)	Female Adult	14-Apr-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TEM0788188	40	Year(s)	Female Adult	14-Apr-98	HIVES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0788464	40	Year(s)	Female Adult	15-Apr-98	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PET0788362		Unknown	Female Adult	15-Apr-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REF0788564		Unknown	Female Adult	16-Apr-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0788704	36	Year(s)	Female Adult	16-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0788543		Unknown	Female Adult	16-Apr-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLI0788709	30	Year(s)	Female Adult	16-Apr-98	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0788680	45	Unknown	Female Adult	16-Apr-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0788764	47	Year(s)	Female Adult	17-Apr-98	PIMPLES	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ODE0788914		Unknown	Unknown	17-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0789024	37	Year(s)	Female Adult	20-Apr-98	PIMPLES	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SUT0789099	46	Year(s)	Female Adult	20-Apr-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0789336		Unknown	Female Adult	21-Apr-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DI 0789357		Unknown	Female Adult	21-Apr-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLA0789604		Unknown	Unknown	22-Apr-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0789739	72	Year(s)	Female Adult	22-Apr-98	WELTS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GUE0790170	26	Year(s)	Female Adult	24-Apr-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0790504	52	Year(s)	Female Adult	27-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PIE0790524	60	Year(s)	Female Adult	27-Apr-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RUS0790400		Unknown	Female Adult	27-Apr-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SER0790610		Unknown	Male Adult	27-Apr-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FEL0790720	41	Year(s)	Female Adult	28-Apr-98	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRL0790819		Unknown	Female Adult	28-Apr-98	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WEI0790880		Unknown	Unknown	28-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	YEO0790666		Unknown	Unknown	28-Apr-98	RASH	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BRO0790992		Unknown	Unknown	29-Apr-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0790982	67	Year(s)	Female Adult	29-Apr-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DOU0791728	49	Year(s)	Female Adult	04-May-98	SWELLING	US	N	SKIN	10	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HYB0791658		Unknown	Female Adult	04-May-98	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHE0791584		Unknown	Female Adult	04-May-98	BUMPS	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOL0791743		Unknown	Female Adult	04-May-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOE0791606		Unknown	Female Adult	04-May-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OES0791585		Unknown	Female Adult	04-May-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	POO0791882	40	Year(s)	Female Adult	04-May-98	REDNESS	US	N	SKIN	3	Day(s)

AGE DEFYING SERIES CREAM PACKETTE	GRA0792075	39	Year(s)	Female Adult	05-May-98	SWELLING	US	Y	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DUP0792220	48	Year(s)	Female Adult	06-May-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FEN0792225		Unknown	Female Adult	06-May-98	BUMPS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0792361		Unknown	Unknown	06-May-98	BOILS	US	Y	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0792282	38	Year(s)	Female Adult	06-May-98	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	SIT0792396	41	Year(s)	Male Adult	06-May-98	BLISTERS	US	Y	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAR0792503		Unknown	Female Adult	07-May-98	RASH	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	SIE0792453		Unknown	Female Adult	07-May-98	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRE0792711	26	Year(s)	Female Adult	08-May-98	PIMPLES	CA	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRU0792955		Unknown	Female Adult	11-May-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	SIN0793051		Unknown	Female Adult	11-May-98	PIMPLES	US	Y	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SPI0792830		Unknown	Female Adult	11-May-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COT0793092		Unknown	Female Adult	12-May-98	DRYNESS	US	N	SKIN	2	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0793159	22	Year(s)	Male Adult	12-May-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAG0793135		Unknown	Unknown	12-May-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLE0793376	27	Year(s)	Female Adult	13-May-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RUS0793396	72	Year(s)	Female Adult	13-May-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHO0793295		Unknown	Female Adult	13-May-98	ACNE	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0793330		Unknown	Unknown	13-May-98	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0793488	33	Year(s)	Female Adult	14-May-98	PEELING	CA	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AWA0793749		Unknown	Female Adult	15-May-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	THO0794188		Unknown	Female Adult	19-May-98	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUC0794588		Unknown	Female Adult	21-May-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAP0794753		Unknown	Unknown	22-May-98	TINGLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VAC0794748	43	Year(s)	Female Adult	22-May-98	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOW0794962		Unknown	Female Adult	26-May-98	PIMPLES	US	N	SKIN	14	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAL0795103		Unknown	Female Adult	26-May-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAD0795113		Unknown	Female Adult	26-May-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ARN0795378	34	Year(s)	Female Adult	27-May-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRO0795223	50	Year(s)	Female Adult	27-May-98	PIMPLES	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NOR0795413		Unknown	Male Adult	27-May-98	ALLERGIC REACTION	US	Y	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0795305		Unknown	Female Adult	27-May-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIR0795507	39	Year(s)	Female Adult	28-May-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LUS0795553	15	Year(s)	004	28-May-98	ACNE	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	COB0795810	42	Year(s)	Female Adult	29-May-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOF0795646	31	Year(s)	Female Adult	29-May-98	SWELLING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0795667		Unknown	Female Adult	29-May-98	REDNESS	US	Y	SKIN	3	Months(s)

OLAY DAILY RENEWAL CREAM 2 OZ	FIT0796031		Unknown	Female Adult	01-Jun-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LIN0796249	42	Year(s)	Female Adult	02-Jun-98	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RAM0796251		Unknown	Female Adult	02-Jun-98	DRYNESS	US	N	SKIN	6	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHA0796265		Unknown	Female Adult	02-Jun-98	SORENESS	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STR0796747		Unknown	Female Adult	04-Jun-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AVE0796776		Unknown	Female Adult	05-Jun-98	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIR0796913		Unknown	Female Adult	05-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NAQ0796841	27	Year(s)	Female Adult	05-Jun-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0797145		Unknown	Unknown	08-Jun-98	(GENERALIZED)	US	N	INHALATION		
AGE DEFYING SERIES CREAM PACKETTE	ROO0797407	40	Year(s)	Female Adult	09-Jun-98	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HER0797456		Unknown	Female Adult	09-Jun-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0797316	24	Year(s)	Female Adult	09-Jun-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0797388		Unknown	Male Adult	09-Jun-98	SUNBURN	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0797629	50	Year(s)	Female Adult	10-Jun-98	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HON0797476		Unknown	Female Adult	10-Jun-98	REDNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STR0797542		Unknown	Female Adult	10-Jun-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0797835		Unknown	Female Adult	11-Jun-98	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CZI0797935		Unknown	Female Adult	12-Jun-98	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	COY0798043		Unknown	Female Adult	12-Jun-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0798264		Unknown	Female Adult	15-Jun-98	PEELING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KEN0798412		Unknown	Female Adult	16-Jun-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ESK0798393		Unknown	Female Adult	16-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0798556		Unknown	Female Adult	16-Jun-98	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KNO0798560		Unknown	Female Adult	16-Jun-98	INFECTION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	SOL0798742		Unknown	Male Adult	17-Jun-98	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAR0799214		Unknown	Female Adult	19-Jun-98	BUMPS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOP0799210		Unknown	Female Adult	19-Jun-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0799092		Unknown	Female Adult	19-Jun-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUC0799075		Unknown	Female Adult	19-Jun-98	ACNE	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIZ0799570		Unknown	Female Adult	23-Jun-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FON0799986		Unknown	Female Adult	25-Jun-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0800141		Unknown	Female Adult	25-Jun-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOG0800323		Unknown	Male Adult	26-Jun-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEL0800761		Unknown	Female Adult	30-Jun-98	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LA 0800801	26	Year(s)	Female Adult	30-Jun-98	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JEP0801648		Unknown	Female Adult	06-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOS0801672	47	Year(s)	Male Adult	06-Jul-98	BLISTERS	US	Y	SKIN	5	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	MOR0801639		Unknown	Unknown	06-Jul-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ALB0801906		Unknown	Female Adult	07-Jul-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	DUC0801813	35	Year(s)	Female Adult	07-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0801743	57	Year(s)	Female Adult	07-Jul-98	STINGING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0803080		Unknown	Female Adult	13-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOS0803347	48	Year(s)	Female Adult	14-Jul-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSK0803346		Unknown	Female Adult	14-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SIR0803507	47	Year(s)	Female Adult	15-Jul-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DI 0803710	45	Year(s)	Female Adult	16-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIT0803730		Unknown	Female Adult	16-Jul-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUM0803832	36	Year(s)	Female Adult	16-Jul-98	CRACKING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REV0803990		Unknown	Female Adult	17-Jul-98	SWELLING	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0804389		Unknown	Female Adult	20-Jul-98	STINGING	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	LYS0804358	73	Year(s)	Female Adult	20-Jul-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARA0804938		Unknown	Female Adult	22-Jul-98	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STO0804930		Unknown	Female Adult	22-Jul-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEN0805313		Unknown	Female Adult	23-Jul-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0805096		Unknown	Female Adult	23-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NET0805985		Unknown	Female Adult	28-Jul-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SON0806436		Unknown	Female Adult	29-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ALT0806606		Unknown	Female Adult	30-Jul-98	ALLERGIC REACTION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RAN0807650		Unknown	Female Adult	05-Aug-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUT0808111		Unknown	Female Adult	07-Aug-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0808754		Unknown	Female Adult	11-Aug-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VAL0808796		Unknown	Female Adult	11-Aug-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	JEC0808929		Unknown	Female Adult	12-Aug-98	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0808995	62	Year(s)	Female Adult	12-Aug-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0809214		Unknown	Unknown	13-Aug-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOE0809346		Unknown	Female Adult	13-Aug-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0809667	46	Year(s)	Female Adult	17-Aug-98	CRACKING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SKA0809851		Unknown	Female Adult	17-Aug-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUR0809991		Unknown	Female Adult	18-Aug-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAN0810020	23	Year(s)	Female Adult	18-Aug-98	HIVES	US	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	UNK0810587	45	Year(s)	Female Adult	20-Aug-98	SWELLING	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAB0811330		Unknown	Female Adult	25-Aug-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FOR0811566	67	Year(s)	Female Adult	26-Aug-98	WELTS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOD0811478		Unknown	Female Adult	26-Aug-98	SNEEZING	US	N	INHALATION		

OLAY DAILY RENEWAL CREAM 2 OZ	LAR0811718		Unknown	Female Adult	27-Aug-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0812052	35	Year(s)	Female Adult	28-Aug-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OUL0811940	54	Year(s)	Female Adult	28-Aug-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEC0812591		Unknown	Male Adult	01-Sep-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOD0812681		Unknown	Female Adult	02-Sep-98	REDNESS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0812740		Unknown	Female Adult	02-Sep-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REH0812654	42	Year(s)	Female Adult	02-Sep-98	RASH	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ELL0813232		Unknown	Female Adult	04-Sep-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0813607	44	Year(s)	Female Adult	08-Sep-98	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CRO0813325	53	Year(s)	Female Adult	08-Sep-98	SWELLING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRE0813404		Unknown	Female Adult	08-Sep-98	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0813724	80	Year(s)	Female Adult	09-Sep-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0813827		Unknown	Female Adult	10-Sep-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALL0814037		Unknown	Female Adult	11-Sep-98	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	YER0814327	57	Year(s)	Female Adult	14-Sep-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOR0814344	43	Year(s)	Female Adult	14-Sep-98	DRYNESS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DIC0814274		Unknown	Female Adult	14-Sep-98	SCRATCH	US	N	INJURY	14	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EWA0814396	41	Year(s)	Female Adult	14-Sep-98	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VAN0814287		Unknown	Female Adult	14-Sep-98	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PHI0814857	44	Year(s)	Female Adult	16-Sep-98	BLISTERS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FOS0814995		Unknown	Female Adult	17-Sep-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHA0815048		Unknown	Female Adult	17-Sep-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0815378		Unknown	Female Adult	21-Sep-98	REDNESS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHE0815578		Unknown	Female Adult	22-Sep-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	.0815836		Unknown	Female Adult	23-Sep-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0815890		Unknown	Female Adult	23-Sep-98	PIMPLES	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIE0815914	65	Year(s)	Female Adult	24-Sep-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VUK0816071		Unknown	Female Adult	24-Sep-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0816254	48	Year(s)	Female Adult	25-Sep-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0816166	35	Year(s)	Female Adult	25-Sep-98	ACNE	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAE0816581	40	Year(s)	Female Adult	29-Sep-98	RASH	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEM0816908	75	Year(s)	Female Adult	30-Sep-98	DISCOLORATION	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUN0817148		Unknown	Unknown	02-Oct-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WES0817485	34	Year(s)	Female Adult	05-Oct-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRE0817962	82	Year(s)	Female Adult	07-Oct-98	SWELLING	US	Y	SKIN	10	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0817858		Unknown	Female Adult	07-Oct-98	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUC0817926		Unknown	Female Adult	07-Oct-98	ACNE	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	CLA0818118		Unknown	Female Adult	08-Oct-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HEI0818330		Unknown	Female Adult	09-Oct-98	ITCHING	US	N	INHALATION	30	002
OLAY DAILY RENEWAL CREAM 2 OZ	KAN0818399		Unknown	Female Adult	09-Oct-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0818345	28	Year(s)	Female Adult	09-Oct-98	DISCOLORATION	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOO0818568	53	Year(s)	Female Adult	12-Oct-98	WRINKLES	US	N	SKIN	1.5	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TEM0819009		Unknown	Female Adult	14-Oct-98	SWELLING	US	N	SKIN	6	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHA0819198		Unknown	Unknown	15-Oct-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0819555	45	Year(s)	Female Adult	19-Oct-98	SWELLING	US	N	SKIN	3.3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0819922		Unknown	Female Adult	20-Oct-98	SWELLING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	PRA0819960		Unknown	Female Adult	20-Oct-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEG0819874		Unknown	Female Adult	20-Oct-98	CONGESTION	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0820612		Unknown	Female Adult	23-Oct-98	DRYNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAN0820546	63	Year(s)	Female Adult	23-Oct-98	BLEMISHES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	LOU0820769		Unknown	Female Adult	26-Oct-98	DRYNESS	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	WOR0821074		Unknown	Female Adult	27-Oct-98	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0821284	34	Year(s)	Female Adult	28-Oct-98	BUMPS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CRU0822438		Unknown	Female Adult	04-Nov-98	FLAKING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0823283	38	Year(s)	Female Adult	09-Nov-98	BUMPS	CA	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	MAS0823478		Unknown	Female Adult	10-Nov-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUR0823399		Unknown	Female Adult	10-Nov-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FUR0823419		Unknown	Unknown	10-Nov-98	PIMPLES	US	N	SKIN	3.5	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAW0823467	72	Year(s)	Female Adult	10-Nov-98	TEARING	CA	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0823709	89	Year(s)	Female Adult	11-Nov-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0823617		Unknown	Female Adult	11-Nov-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DOY0823650		Unknown	Female Adult	11-Nov-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	EVE0823633		Unknown	Female Adult	11-Nov-98	RASH	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0823843	21	Year(s)	Female Adult	12-Nov-98	PIMPLES	CA	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0823868	66	Year(s)	Female Adult	12-Nov-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MON0823860	27	Year(s)	Female Adult	12-Nov-98	SWELLING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOM0824084	62	Year(s)	Female Adult	13-Nov-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	GEL0824137		Unknown	Unknown	13-Nov-98	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0824211		Unknown	Female Adult	13-Nov-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0824422		Unknown	Female Adult	16-Nov-98	BURNING	US	Y	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOD0825093		Unknown	Female Adult	18-Nov-98	DERMATITIS	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUM0824894	42	Year(s)	Female Adult	18-Nov-98	PIMPLES	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	SCH0825496		Unknown	Female Adult	20-Nov-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	HOU0825809		Unknown	Female Adult	23-Nov-98	SORES	US	N	SKIN	2	Months(s)

OLAY DAILY RENEWAL CREAM 2 OZ	MAR0825563	38	Year(s)	Female Adult	23-Nov-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0825784	25	Year(s)	Female Adult	23-Nov-98	FLAKING	US	N	SKIN	5	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RUE0826459	40	Year(s)	Female Adult	30-Nov-98	SWELLING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0826811	82	Year(s)	Female Adult	01-Dec-98	SWEAT	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	SAM0826784		Unknown	Unknown	01-Dec-98	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SNO0826759		Unknown	Female Adult	01-Dec-98	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0826771		Unknown	Female Adult	01-Dec-98	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	EOP0827007	50	Year(s)	Female Adult	02-Dec-98	SWELLING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAM0826995		Unknown	Female Adult	02-Dec-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0827160	75	Year(s)	Female Adult	03-Dec-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0827168	35	Year(s)	Female Adult	03-Dec-98	SWELLING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0827358		Unknown	Female Adult	04-Dec-98	FLUSHED	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0827500		Unknown	Unknown	04-Dec-98	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PRE0827504		Unknown	Female Adult	04-Dec-98	REDNESS	CA	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ESA0827735	33	Year(s)	Female Adult	07-Dec-98	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COT0828028	22	Year(s)	Female Adult	08-Dec-98	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIR0827885	26	Year(s)	Female Adult	08-Dec-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAM0828235		Unknown	Male Adult	09-Dec-98	WRINKLES	US	N	SKIN	9	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AZI0828406		Unknown	Female Adult	10-Dec-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAW0828285	74	Year(s)	Female Adult	10-Dec-98	FLAKING	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCH0828936		Unknown	Female Adult	14-Dec-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0828741	34	Year(s)	Female Adult	14-Dec-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PER0829110	24	Year(s)	Female Adult	15-Dec-98	PIMPLES	CA	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0829010		Unknown	Female Adult	15-Dec-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NIC0829193	46	Year(s)	Female Adult	16-Dec-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GID0829376		Unknown	Female Adult	17-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MC 0829875	57	Year(s)	Female Adult	21-Dec-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0829794		Unknown	Female Adult	21-Dec-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0829933		Unknown	Female Adult	21-Dec-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ANK0830303		Unknown	Unknown	28-Dec-98	IRRITATION	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0830621		Unknown	Female Adult	28-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0830544	39	Year(s)	Male Adult	28-Dec-98	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0830544	39	Year(s)	Male Adult	28-Dec-98	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEN0831353		Unknown	Female Adult	04-Jan-99	STINGING	US	N	INHALATION	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	MCL0831283	37	Year(s)	Female Adult	04-Jan-99	DRYNESS	CA	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VIS0831523		Unknown	Female Adult	05-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0831886		Unknown	Female Adult	06-Jan-99	DRYNESS	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	PRI0832017		Unknown	Female Adult	06-Jan-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ECK0832092		Unknown	Unknown	07-Jan-99	SNEEZING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	FOS0832158		Unknown	Male Adult	07-Jan-99	SWELLING	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HER0832162	44	Year(s)	Female Adult	07-Jan-99	PIMPLES	US	N	SKIN	11	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0832249	40	Year(s)	Female Adult	07-Jan-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CUR0832392		Unknown	Female Adult	08-Jan-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0832305	29	Year(s)	Female Adult	08-Jan-99	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEA0832723		Unknown	Female Adult	11-Jan-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RAY0832548	30	Year(s)	Female Adult	11-Jan-99	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAE0832749		Unknown	Female Adult	11-Jan-99	PEELING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	REI0832607		Unknown	Female Adult	11-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AIK0833066	35	Year(s)	Female Adult	12-Jan-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAS0833239	70	Year(s)	Female Adult	13-Jan-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0833636	39	Year(s)	Female Adult	15-Jan-99	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	FAU0833820	70	Year(s)	Female Adult	19-Jan-99	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIU0833724		Unknown	Female Adult	19-Jan-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0834133		Unknown	Female Adult	20-Jan-99	HIVES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0834312		Unknown	Female Adult	20-Jan-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRU0834260	71	Year(s)	Female Adult	20-Jan-99	BLEMISHES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BEL0834463	25	Year(s)	Female Adult	21-Jan-99	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0834497		Unknown	Female Adult	21-Jan-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0834560		Unknown	Female Adult	21-Jan-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FRA0834616		Unknown	Female Adult	22-Jan-99	BLISTERS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0834715		Unknown	Female Adult	22-Jan-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAY0834883		Unknown	Female Adult	25-Jan-99	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAL0834930		Unknown	Female Adult	25-Jan-99	RASH	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KUN0835417	45	Year(s)	Female Adult	27-Jan-99	HEADACHE	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FIL0835790		Unknown	Female Adult	28-Jan-99	BURN	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SAU0835664	42	Year(s)	Female Adult	28-Jan-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEM0835831		Unknown	Female Adult	28-Jan-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAM0835819	52	Year(s)	Female Adult	28-Jan-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0835722	70	Year(s)	Female Adult	28-Jan-99	REDNESS	CA	N	EYE	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAL0835960	64	Year(s)	Female Adult	29-Jan-99	REDNESS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOE0835856		Unknown	Female Adult	29-Jan-99	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ACK0836091	78	Year(s)	Female Adult	01-Feb-99	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	EDI0836304		Unknown	Male Adult	01-Feb-99	RASH	US	N	SKIN	15	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0836241	70	Year(s)	Female Adult	01-Feb-99	DRYNESS	US	N	SKIN	2	Day(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEO0836380	44	Year(s)	Female Adult	02-Feb-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COU0836401		Unknown	Female Adult	02-Feb-99	DISCOLORATION	US	N	SKIN	4	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0836388	51	Year(s)	Female Adult	02-Feb-99	OTHER	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAC0836714	44	Year(s)	Female Adult	03-Feb-99	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KUN0837062		Unknown	Female Adult	04-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEM0836942		Unknown	Unknown	04-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEX0836929		Unknown	Female Adult	04-Feb-99	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SMI0837249		Unknown	Female Adult	05-Feb-99	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0837287	41	Year(s)	Female Adult	05-Feb-99	REDNESS	CA	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OLS0837289	68	Year(s)	Female Adult	05-Feb-99	REDNESS	US	N	EYE	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0837288		Unknown	Female Adult	05-Feb-99	RASH	US	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIR0837373	29	Year(s)	Female Adult	08-Feb-99	REDNESS	CA	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRU0837948		Unknown	Female Adult	10-Feb-99	DRYNESS	US	N	EYE	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COM0837957	69	Year(s)	Female Adult	10-Feb-99	HIVES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FLA0837945		Unknown	Female Adult	10-Feb-99	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TID0838131		Unknown	Female Adult	10-Feb-99	BUMPS	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	URS0838249		Unknown	Female Adult	11-Feb-99	BURNING	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAT0838210	67	Year(s)	Female Adult	11-Feb-99	DIFFICULTY	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	LAR0838327		Unknown	Female Adult	11-Feb-99	REDNESS	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GRA0838626		Unknown	Female Adult	16-Feb-99	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	VIN0838710		Unknown	Female Adult	16-Feb-99	CRACKING	US	N	SKIN	6	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEI0838942	43	Year(s)	Female Adult	17-Feb-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ADI0839116	40	Year(s)	Female Adult	17-Feb-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0839298	33	Year(s)	Female Adult	18-Feb-99	SWELLING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PER0839149	52	Year(s)	Female Adult	18-Feb-99	BUMPS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOL0839374	22	Year(s)	Female Adult	18-Feb-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PAR0839908	50	Year(s)	Female Adult	22-Feb-99	BURNING	CA	N	SKIN	14	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0839930		Unknown	Female Adult	22-Feb-99	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEA0840065		Unknown	Female Adult	23-Feb-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	YAN0840329		Unknown	Female Adult	24-Feb-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0840523	42	Year(s)	Female Adult	25-Feb-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAK0840684	78	Year(s)	Female Adult	25-Feb-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HEA0840933		Unknown	Female Adult	26-Feb-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAL0841238	36	Year(s)	Female Adult	01-Mar-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BHA0841146		Unknown	Male Adult	01-Mar-99	DISCOLORATION	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0841047		Unknown	Female Adult	01-Mar-99	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	STA0841250	70	Year(s)	Female Adult	01-Mar-99	PIMPLES	US	Y	SKIN	2	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DOM0841410		Unknown	Unknown	02-Mar-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAL0841438	55	Year(s)	Female Adult	02-Mar-99	DIZZINESS	CA	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLO0841753		Unknown	Female Adult	03-Mar-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NUT0842102		Unknown	Female Adult	05-Mar-99	SWELLING	US	N	SKIN		Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOI0842392	49	Year(s)	Female Adult	08-Mar-99	BURNING	US	N	SKIN	9	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PET0842547	50	Year(s)	Female Adult	08-Mar-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SNE0842552		Unknown	Male Adult	08-Mar-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0842473	31	Year(s)	Female Adult	08-Mar-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SWE0842482	44	Year(s)	Female Adult	08-Mar-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAY0842821		Unknown	Female Adult	09-Mar-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEN0842860		Unknown	Female Adult	09-Mar-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0842921	51	Year(s)	Female Adult	09-Mar-99	DRYNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUF0843123		Unknown	Unknown	10-Mar-99	PEELING	CA	N	SKIN		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUM0843051	64	Year(s)	Female Adult	10-Mar-99	SWELLING	CA	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COL0843462		Unknown	Unknown	11-Mar-99	REDNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAF0843452		Unknown	Unknown	11-Mar-99	BURNING	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOS0843567		Unknown	Female Adult	12-Mar-99	FLAKING	US	N	SKIN	2	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DED0843610		Unknown	Female Adult	12-Mar-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0843667		Unknown	Female Adult	12-Mar-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0843735		Unknown	Female Adult	12-Mar-99	RASH	US	N	SKIN	5	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	SAN0843988		Unknown	004	15-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0844002		Unknown	Female Adult	15-Mar-99	BUMPS	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAL0843840	68	Year(s)	Female Adult	15-Mar-99	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OLI0843945		Unknown	Female Adult	15-Mar-99	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0844221		Unknown	Female Adult	16-Mar-99	BURNING	US	N	EYE INDIRECT	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0844501	71	Year(s)	Female Adult	17-Mar-99	WRINKLES	US	N	SKIN		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAL0844711		Unknown	Female Adult	18-Mar-99	SWELLING	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUN0844716		Unknown	Unknown	18-Mar-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0845002		Unknown	Female Adult	19-Mar-99	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ADA0845623	40	Year(s)	Female Adult	23-Mar-99	ACNE	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TOR0845733		Unknown	Female Adult	23-Mar-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIT0845774	76	Year(s)	Unknown	23-Mar-99	REDNESS	US	Y	EYE INDIRECT	8	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIO0845575	51	Year(s)	Female Adult	23-Mar-99	DRYNESS	CA	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLA0846020	22	Year(s)	Female Adult	24-Mar-99	RASH	CA	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0846228		Unknown	Unknown	25-Mar-99	INFLAMED	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAH0846355	50	Year(s)	Female Adult	26-Mar-99	BUMPS	CA	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAT0846995	59	Year(s)	Female Adult	30-Mar-99	CHAPPED	US	N	SKIN		

AGE DEFYING SERIES CREAM PACKETTE	REF0847434		Unknown	004	31-Mar-99	RASH	US	N	SKIN	12	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEI0847388		Unknown	Female Adult	31-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0847609		Unknown	Female Adult	01-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAT0847731	43	Year(s)	Female Adult	05-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	YOU0848463	45	Year(s)	Male Adult	07-Apr-99	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0848515		Unknown	Unknown	08-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FRE0848672	44	Year(s)	Female Adult	08-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEB0848563	32	Year(s)	Female Adult	08-Apr-99	BUMPS	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NEL0848827			Female Adult	09-Apr-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STE0849006		Unknown	Female Adult	12-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HER0848974		Unknown	Female Adult	12-Apr-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CIC0849479		Unknown	Female Adult	13-Apr-99	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOO0849462		Unknown	Female Adult	13-Apr-99	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0849296	64	Year(s)	Female Adult	13-Apr-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ULL0849706		Unknown	Male Adult	14-Apr-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0849899		Unknown	Female Adult	15-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0849834		Unknown	Unknown	15-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ILV0849960	40	Year(s)	Male Adult	15-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0849802		Unknown	Female Adult	15-Apr-99	BLEMISHES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0850400	70	Year(s)	Female Adult	19-Apr-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAD0850591		Unknown	Female Adult	19-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LAC0850335		Unknown	Female Adult	19-Apr-99	FLAKING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0850373	66	Year(s)	Female Adult	19-Apr-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ECH0850802		Unknown	Female Adult	20-Apr-99	REDNESS	US	N	SKIN	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	PRI0850632		Unknown	Female Adult	20-Apr-99	RASH	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRU0850889		Unknown	Female Adult	21-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TOW0853962			Female Adult	21-Apr-99	BURNING	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCH0851733		Unknown	Female Adult	26-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BLE0851550		Unknown	Female Adult	26-Apr-99	SWELLING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	AME0851893		Unknown	Female Adult	27-Apr-99	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEN0851953	31	Year(s)	Female Adult	27-Apr-99	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0852048		Unknown	Female Adult	27-Apr-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FAL0852139		Unknown	Female Adult	28-Apr-99	BURNING	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAL0852359	51	Year(s)	Female Adult	29-Apr-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0852526		Unknown	Female Adult	29-Apr-99	REDNESS	US	N	EYE		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0852923	50	Year(s)	Female Adult	03-May-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROG0852933		Unknown	Female Adult	03-May-99	PIMPLES	US	N	SKIN	1	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VAI0853218	65	Year(s)	Female Adult	04-May-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PER0853144		Unknown	Female Adult	04-May-99	RASH	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0853417		Unknown	Female Adult	05-May-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MOY0853863		Unknown	Female Adult	07-May-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0853755	59	Year(s)	Female Adult	07-May-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LA 0854266		Unknown	Female Adult	10-May-99	REDNESS	US	N	SKIN	15	002
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ESC0854421		Unknown	Female Adult	11-May-99	BOILS	US	N	SKIN	6	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAR0854583		Unknown	Female Adult	12-May-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUI0854650		Unknown	Female Adult	12-May-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0854662		Unknown	Female Adult	12-May-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GER0854915	39	Year(s)	Female Adult	13-May-99	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SIE0854984		Unknown	Unknown	14-May-99	REDNESS	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROB0856171		Unknown	Unknown	20-May-99	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0856637	41	Year(s)	Female Adult	24-May-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NEI0857662		Unknown	Female Adult	28-May-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KOH0857978		Unknown	Male Adult	01-Jun-99	DERMATITIS	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAL0858334	80	Year(s)	Female Adult	03-Jun-99	PEELING	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TYL0858396		000	Unknown	03-Jun-99	BURNING	US	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEM0858624	65	Year(s)	Female Adult	04-Jun-99	TINGLING	US	N	SKIN	4	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEY0858688		Unknown	Female Adult	04-Jun-99	PIMPLES	US	Y	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JIN0858587		Unknown	Female Adult	04-Jun-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ANT0859007			Female Adult	07-Jun-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DUC0859081	49	Year(s)	Female Adult	07-Jun-99	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUL0859255	40	Year(s)	Female Adult	08-Jun-99	BLISTERS	US	Y	SKIN	8	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAT0859532		Unknown	Female Adult	10-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	POR0860202		Unknown	Female Adult	14-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	THO0860054		Unknown	Female Adult	14-Jun-99	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0859985		Unknown	Female Adult	14-Jun-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0860797		Unknown	Female Adult	17-Jun-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0861641	62	Year(s)	Female Adult	23-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SES0861857		Unknown	Unknown	24-Jun-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAY0861968	35	Year(s)	Female Adult	24-Jun-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KEL0862119		Unknown	Female Adult	25-Jun-99	PIMPLES	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STA0862207		Unknown	Female Adult	25-Jun-99	TIGHTNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAN0862782		Unknown	Female Adult	29-Jun-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	QUE0862715		Unknown	Female Adult	29-Jun-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUN0862747		Unknown	Male Adult	29-Jun-99	RASH	US	Y	SKIN	1	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GAR0862983	69	Year(s)	Female Adult	30-Jun-99	REDNESS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0862984		Unknown	Female Adult	30-Jun-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0863075		Unknown	Female Adult	01-Jul-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUG0863523		Unknown	Female Adult	06-Jul-99	BURNING	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REF0863784		Unknown	Female Adult	07-Jul-99	PEELING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SHA0863745		Unknown	Female Adult	07-Jul-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CRC0863731	58	Year(s)	Female Adult	07-Jul-99	CUT	CA	N	INJURY		
OLAY DAILY RENEWAL CREAM 2 OZ	TOR0864233		Unknown	Female Adult	09-Jul-99	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AND0864546		Unknown	Female Adult	12-Jul-99	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FUL0865062		Unknown	Female Adult	15-Jul-99	BURNING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REI0865678			Female Adult	19-Jul-99	CYST	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIS0865850		Unknown	Male Adult	20-Jul-99	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAL0865842	57	Year(s)	Female Adult	20-Jul-99	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POT0866394	60	Year(s)	Female Adult	23-Jul-99	TEARING	CA	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	AHN0866960	32	Year(s)	004	27-Jul-99	ITCHING	CA	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KLE0867801		Unknown	Female Adult	02-Aug-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	OSB0867673	72	Year(s)	Female Adult	02-Aug-99	BURNING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0868000		Unknown	Female Adult	03-Aug-99	BURNING	US	N	EYE INDIRECT	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAU0868536		Unknown	Female Adult	06-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSE0868467	34	Year(s)	Female Adult	06-Aug-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUC0868611		Unknown	Female Adult	06-Aug-99	BURNING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOL0868795		Unknown	Female Adult	09-Aug-99	PIMPLES	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VER0869126		Unknown	Female Adult	10-Aug-99	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THA0870027		Unknown	Female Adult	17-Aug-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0870285		Unknown	Female Adult	19-Aug-99	STINGING/BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BEA0870497		Unknown	Unknown	20-Aug-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCO0870550		Unknown	Female Adult	20-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WER0870459		Unknown	Female Adult	20-Aug-99	IRRITATION	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NGU0870800	30	Year(s)	Female Adult	23-Aug-99	SWELLING	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAS0871244		Unknown	Female Adult	25-Aug-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STE0871556		Unknown	Female Adult	27-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAU0872089		Unknown	Female Adult	31-Aug-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VER0872143		Unknown	Female Adult	31-Aug-99	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NAZ0872526	53	Year(s)	Female Adult	02-Sep-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0872519		Unknown	Female Adult	02-Sep-99	ITCHING	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0872525		Unknown	Female Adult	02-Sep-99	BURNING	US	N	SKIN	3	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0872775		Unknown	Female Adult	03-Sep-99	STINGING	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	WAG0872679		Unknown	Female Adult	03-Sep-99	ITCHING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIV0872988		Unknown	Female Adult	07-Sep-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TIN0873345	40	Year(s)	Female Adult	09-Sep-99	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	GER0874057		Unknown	Female Adult	14-Sep-99	DIFFICULTY	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUR0874377	75	Year(s)	Female Adult	15-Sep-99	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KNA0874326		Unknown	Unknown	15-Sep-99	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUN0874557		Unknown	Female Adult	16-Sep-99	RASH	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CLE0874910		Unknown	Female Adult	20-Sep-99	BURNING	US	N	SKIN	6	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DER0874976	64	Year(s)	Female Adult	20-Sep-99	SORENESS	CA	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STE0874802		Unknown	Female Adult	20-Sep-99	HEADACHE	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOR0875343		Unknown	Female Adult	22-Sep-99	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	CAS0875443		Unknown	Female Adult	22-Sep-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ELM0875307	73	Year(s)	Female Adult	22-Sep-99	BURNING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0875405	71	Year(s)	Female Adult	22-Sep-99	BURNING	US	N	SKIN		Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROT0875930		Unknown	Female Adult	27-Sep-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0876617		Unknown	Female Adult	30-Sep-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	HOS0876778		Unknown	Female Adult	01-Oct-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALM0876756	36	Year(s)	Female Adult	01-Oct-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LAU0877033		Unknown	Female Adult	04-Oct-99	PEELING	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOS0877398		Unknown	Male Adult	05-Oct-99	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0877476		Unknown	Female Adult	06-Oct-99	SWELLING	US	N	SKIN	1	007
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0877476		Unknown	Female Adult	06-Oct-99	SWELLING	US	N	SKIN	1	007
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0877689		Unknown	Female Adult	07-Oct-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEV0877970		Unknown	Female Adult	08-Oct-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COZ0878396		Unknown	Female Adult	12-Oct-99	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0878455		Unknown	Female Adult	12-Oct-99	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FER0878654		Unknown	Female Adult	13-Oct-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0878890	64	Year(s)	Female Adult	14-Oct-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOD0879203			Female Adult	18-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CRU0879572		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STO0879493		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAT0879525		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRU0879965		Unknown	Female Adult	21-Oct-99	BURNING	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOO0880087	33	Year(s)	Female Adult	22-Oct-99	BURNING	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0880130		Unknown	Female Adult	22-Oct-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOO0880645		Unknown	Female Adult	26-Oct-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAR0880881	83	Year(s)	Female Adult	28-Oct-99	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	BIS0881294		Unknown	Female Adult	01-Nov-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEA0882321		Unknown	Female Adult	08-Nov-99	STINGING/BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAN0882687		Unknown	Female Adult	09-Nov-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0883011		Unknown	Female Adult	11-Nov-99	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COL0883963		Unknown	Female Adult	17-Nov-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LOG0884236		Unknown	Female Adult	18-Nov-99	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAS0884345		Unknown	Female Adult	19-Nov-99	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAG0884302	44	Year(s)	Female Adult	19-Nov-99	PIMPLES	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DEP0884738		Unknown	Female Adult	23-Nov-99	REDNESS	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PHI0884919		Unknown	Female Adult	24-Nov-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0885591		Unknown	Female Adult	30-Nov-99	BURNING	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CUR0885731		Unknown	Female Adult	01-Dec-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RYA0885688		Unknown	Female Adult	01-Dec-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ATW0885817		Unknown	Female Adult	01-Dec-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCA0886016		Unknown	Female Adult	02-Dec-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0886002		Unknown	Male Adult	02-Dec-99	BLISTERS	US	Y	SKIN	10	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0886586		Unknown	Female Adult	07-Dec-99	BLISTERS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOD0886473	62	Year(s)	Female Adult	07-Dec-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PLA0886933	39	Year(s)	Female Adult	09-Dec-99	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COV0887131	45	Year(s)	Male Adult	10-Dec-99	BLISTERS	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOK0887077		Unknown	Female Adult	10-Dec-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRO0887209		Unknown	Female Adult	13-Dec-99	COUGHING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	BAC0887500		Unknown	Female Adult	14-Dec-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DOL0887591		Unknown	Female Adult	15-Dec-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LON0887717		Unknown	Female Adult	15-Dec-99	REDNESS	US	N	SKIN	2	Months(s)
OLAY DAILY RENEWAL LOTION 4 OZ	EMM0888047	36	Year(s)	Female Adult	20-Dec-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0888304		Unknown	Female Adult	21-Dec-99	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COR0888576	66	Year(s)	Female Adult	22-Dec-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SIM0888612		Unknown	Female Adult	22-Dec-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EVA0889072	68	Year(s)	Female Adult	29-Dec-99	BURNING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DIA0889286		Unknown	Female Adult	30-Dec-99	ITCHING	US	Y	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REY0889388		Unknown	Female Adult	30-Dec-99	BURNING	US	N	SKIN	10	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FLE0889597		Unknown	Female Adult	04-Jan-00	BUMPS	US	N	SKIN		Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEB0889955		Unknown	Female Adult	06-Jan-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AND0889927		Unknown	Female Adult	06-Jan-00	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PRE0890074	44	Year(s)	Female Adult	06-Jan-00	SWELLING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0890163		Unknown	Female Adult	07-Jan-00	BURNING	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	PIK0890174		Unknown	Female Adult	07-Jan-00	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STU0890190		Unknown	Female Adult	07-Jan-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	QUI0890595	31	Year(s)	Female Adult	10-Jan-00	UNKNOWN	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AVI0890463	37	Year(s)	Male Adult	10-Jan-00	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEL0890379		Unknown	Female Adult	10-Jan-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0890739	37	Year(s)	Female Adult	11-Jan-00	SWELLING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0890888		Unknown	Female Adult	12-Jan-00	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0890969		000	Male Adult	12-Jan-00	RASH	US	Y	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BRO0891129			Female Adult	13-Jan-00	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0891090		Unknown	Female Adult	13-Jan-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAZ0891831	45	Year(s)	Female Adult	19-Jan-00	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0891668		Unknown	Female Adult	19-Jan-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0891983	56	Year(s)	Female Adult	20-Jan-00	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0892108		Unknown	Female Adult	21-Jan-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0892468		Unknown	Female Adult	24-Jan-00	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0892312		Unknown	Female Adult	24-Jan-00	FLAKING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0892465		Unknown	Female Adult	24-Jan-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BEI0892496		Unknown	Female Adult	25-Jan-00	REDNESS	US	Y	SKIN	4	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	CAP0893201		Unknown	Female Adult	28-Jan-00	TINGLING	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0893294	34	Year(s)	Female Adult	28-Jan-00	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEH0893269		Unknown	Female Adult	28-Jan-00	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0893546		Unknown	Female Adult	31-Jan-00	TEARING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ZIL0893391		Unknown	Female Adult	31-Jan-00	PIMPLES	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0893752	56	Year(s)	Female Adult	01-Feb-00	PIMPLES	US	N	SKIN	3	007
OLAY DAILY RENEWAL CREAM 2 OZ	HEF0893809		Unknown	Female Adult	01-Feb-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SWI0894083		Unknown	Female Adult	02-Feb-00	PIMPLES	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GAR0894117		Unknown	Female Adult	03-Feb-00	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0894230		Unknown	Female Adult	03-Feb-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLA0894493		Unknown	Female Adult	04-Feb-00	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DRA0894521		Unknown	Female Adult	04-Feb-00	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RIT0894708	66	Year(s)	Female Adult	07-Feb-00	SWELLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRE0894777		Unknown	Female Adult	07-Feb-00	SWELLING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CHA0895501		Unknown	Female Adult	10-Feb-00	REDNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOU0895321	39	Year(s)	Female Adult	10-Feb-00	SWELLING	CA	N	SKIN	4	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	MC 0896100	85	Year(s)	Female Adult	15-Feb-00	REDNESS	CA	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOG0896183	33	Year(s)	Female Adult	15-Feb-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIC0896106		Unknown	Female Adult	15-Feb-00	DRYNESS	US	N	SKIN	2	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	WIL0896116		Unknown	Female Adult	15-Feb-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FEN0896292		Unknown	Female Adult	16-Feb-00	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0896509		Unknown	Female Adult	17-Feb-00	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	POP0897097		Unknown	Female Adult	22-Feb-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAI0897260	46	Year(s)	Female Adult	23-Feb-00	BLISTERS	US	N	SKIN	48	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LUB0897532		Unknown	Female Adult	24-Feb-00	SWELLING	US	N	SKIN	10	002
OLAY DAILY RENEWAL CREAM 2 OZ	CRA0897541		Unknown	Female Adult	25-Feb-00	BURNING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FIS0897551	41	Year(s)	Female Adult	25-Feb-00	RASH	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROB0898004		Unknown	Female Adult	28-Feb-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEV0897969		Unknown	Female Adult	28-Feb-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ADA0898034	39	Year(s)	Female Adult	29-Feb-00	BUMPS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SIN0898272		Unknown	Female Adult	01-Mar-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	CRO0898487		Unknown	Female Adult	02-Mar-00	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAZ0898669		Unknown	Female Adult	03-Mar-00	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOR0898783	72	Year(s)	Female Adult	06-Mar-00	BLISTERS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JAC0898942	42	Year(s)	Female Adult	06-Mar-00	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OLS0898959	66	Year(s)	Female Adult	06-Mar-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WOS0899034		Unknown	Female Adult	06-Mar-00	RASH	US	Y	SKIN	9	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LAC0899407	55	Year(s)	Female Adult	08-Mar-00	BURNING	CA	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RUT0899298	45	Year(s)	Female Adult	08-Mar-00	REDNESS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRU0899259		Unknown	Female Adult	08-Mar-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ENG0900063		Unknown	Female Adult	13-Mar-00	REDNESS	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0900159		Unknown	Female Adult	14-Mar-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEN0900591	88	Year(s)	Female Adult	16-Mar-00	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIT0900535		Unknown	Female Adult	16-Mar-00	PIMPLES	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAV0900968	57	Year(s)	Female Adult	20-Mar-00	SWELLING	US	N	SKIN	8	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAV0900897		Unknown	004	20-Mar-00	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SWE0900892		Unknown	Female Adult	20-Mar-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CHI0901136		Unknown	Female Adult	21-Mar-00	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEI0901110		Unknown	Unknown	21-Mar-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRO0901568		Unknown	Female Adult	23-Mar-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0901587	38	Year(s)	Female Adult	23-Mar-00	BURNING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0901536		Unknown	Female Adult	23-Mar-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NAT0901824	44	Year(s)	Female Adult	24-Mar-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MCK0901943	55	Year(s)	Female Adult	27-Mar-00	SWELLING	CA	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0901900	39	Year(s)	Female Adult	27-Mar-00	SWELLING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0902203		Unknown	Female Adult	28-Mar-00	BURNING	US	N	SKIN	3	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	WEI0902175		Unknown	Female Adult	28-Mar-00	SWELLING	CA	N	SKIN	12	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUC0902427		Unknown	Unknown	29-Mar-00	SORENESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0902391		Unknown	Female Adult	29-Mar-00	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EKA0902444		Unknown	Female Adult	29-Mar-00	PIMPLES	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0902812		Unknown	Female Adult	31-Mar-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRO0902813		Unknown	Unknown	31-Mar-00	BURNING	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	MOO0902979	39	Year(s)	Female Adult	03-Apr-00	REDNESS	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAR0903230	72	Year(s)	Female Adult	04-Apr-00	DISCOLORATION	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROG0903417		Unknown	Female Adult	05-Apr-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CO 0903749		Unknown	Female Adult	07-Apr-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DYC0904097	23	Year(s)	Female Adult	10-Apr-00	BUMPS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0904414	68	Year(s)	Female Adult	12-Apr-00	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIT0905179		Unknown	Unknown	18-Apr-00	STINGING	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUK0905354		Unknown	Unknown	19-Apr-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PAQ0905828		Unknown	Female Adult	24-Apr-00	REDNESS	CA	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HER0906019		Unknown	Unknown	25-Apr-00	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAL0905886		Unknown	Female Adult	25-Apr-00	TINGLING	US	N	EYE INDIRECT		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DAV0906134		Unknown	Female Adult	26-Apr-00	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEI0906052		Unknown	Female Adult	26-Apr-00	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEA0906719	80	Year(s)	Female Adult	01-May-00	BURNING	US	N	SKIN	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	ULE0906671	72	Year(s)	Female Adult	01-May-00	RUNNY NOSE	US	N	INHALATION	5	002
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	OET0906916	57	Year(s)	Female Adult	02-May-00	BURNING	US	N	SKIN	36	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REN0906957	76	Year(s)	Female Adult	02-May-00	TEARING	US	N	EYE INDIRECT		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0907292		Unknown	Female Adult	04-May-00	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0907321		Unknown	Female Adult	04-May-00	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUD0907385		Unknown	Female Adult	04-May-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	IAC0907931		Unknown	Female Adult	10-May-00	SWELLING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	HOR0908203		Unknown	Female Adult	11-May-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0908470	6	Unknown	Unknown	12-May-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0909340		Unknown	Female Adult	19-May-00	WELTS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROM0909262	49	Year(s)	Female Adult	19-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAB0910103		Unknown	Female Adult	25-May-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POO0910120	34	Year(s)	Female Adult	25-May-00	ITCHING	CA	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0911064		Unknown	Female Adult	02-Jun-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAA0911089		Unknown	Female Adult	02-Jun-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUL0911285	39	Year(s)	Female Adult	05-Jun-00	BLURRED VISION	US	N	EYE	20	002
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0911208		Unknown	Female Adult	05-Jun-00	WELTS	US	N	SKIN	1	Day(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VON0911504		Unknown	Female Adult	06-Jun-00	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0911465		Unknown	Female Adult	06-Jun-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PIT0911711		Unknown	Unknown	07-Jun-00	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0911637		Unknown	Female Adult	07-Jun-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIL0912325		Unknown	Female Adult	12-Jun-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0912657		Unknown	Female Adult	14-Jun-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAG0913032		Unknown	Female Adult	19-Jun-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0913323		Unknown	Female Adult	21-Jun-00	SORENESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUR0913588	71	Year(s)	Unknown	23-Jun-00	TEARING	US	N	EYE INDIRECT	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SOB0914105		Unknown	Female Adult	28-Jun-00	COUGHING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	STA0914292		Unknown	Female Adult	29-Jun-00	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ACR0914388		Unknown	Female Adult	30-Jun-00	BURNING	US	N	EYE	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAN0914481	33	Year(s)	Female Adult	03-Jul-00	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NEK0914871		Unknown	Unknown	06-Jul-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REE0915150	16	Year(s)	004	10-Jul-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAO0915316			Female Adult	11-Jul-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0916038			Unknown	19-Jul-00	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COX0916223			Unknown	20-Jul-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAN0917668	54	Year(s)	Female Adult	01-Aug-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GIL0917996	80	Year(s)	Female Adult	03-Aug-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAD0918604				09-Aug-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0919142			Unknown	14-Aug-00	BUMPS	US	N	SKIN		
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	AUL0919417			Unknown	16-Aug-00	(GENERALIZED)	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STE0919550			Unknown	17-Aug-00	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ART0919517			Unknown	17-Aug-00	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOY0920176			Unknown	23-Aug-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0920443	58	Year(s)	Female Adult	24-Aug-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ASH0920976	81	Year(s)	Female Adult	29-Aug-00	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KER0921039	58	Year(s)	Female Adult	29-Aug-00	PIMPLES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOB0921070			Unknown	29-Aug-00	HIVES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLE0921176	54	Year(s)	Female Adult	30-Aug-00	BURNING	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DES0921883	70	Year(s)	Female Adult	06-Sep-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0922341				11-Sep-00	WRINKLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RAM0922576	42	Year(s)	Female Adult	12-Sep-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PER0923865	58	Year(s)	Female Adult	21-Sep-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BRU0924730			Unknown	27-Sep-00	BUMPS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FIE0926624			Unknown	09-Oct-00	BUMPS	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0926938			Unknown	11-Oct-00	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BUC0926856	76	Year(s)	Female Adult	11-Oct-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOR0926952	49	Year(s)	Female Adult	11-Oct-00	RASH	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0927227				12-Oct-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MOY0928131			Unknown	18-Oct-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VIE0928437			Unknown	20-Oct-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0928423	52	Year(s)	Female Adult	20-Oct-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0929057			Unknown	24-Oct-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOL0929118	42	Year(s)	Female Adult	25-Oct-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PUE0929212			Unknown	25-Oct-00	PIMPLES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JON0930002			Unknown	31-Oct-00	TEARING	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0930122			Unknown	01-Nov-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0931424			Unknown	01-Nov-00	HIVES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUF0930589	49	Year(s)	Female Adult	02-Nov-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0930799	28	Year(s)	Female Adult	03-Nov-00	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0930693	62	Year(s)	Female Adult	03-Nov-00	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOW0931988	54	Year(s)	Female Adult	10-Nov-00	DISCOLORATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOS0931991	63	Year(s)	Female Adult	10-Nov-00	IRRITATION	US	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0932066	32	Year(s)	Female Adult	10-Nov-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GRE0932240				13-Nov-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CRA0932605			Unknown	14-Nov-00	SORENESS	US	N	EYE		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAY0933324	69	Year(s)	Female Adult	20-Nov-00	TEARING	CA	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HEA0933617				21-Nov-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KIE0933632			Unknown	22-Nov-00	WARM/FLUSHED	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ITU0934970	50	Second(s)	Unknown	04-Dec-00	REDNESS	CA	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEN0934944				04-Dec-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEN0934944				04-Dec-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUF0935078	47	Year(s)	Female Adult	05-Dec-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BUS0935131		Second(s)	Unknown	05-Dec-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0935360		Second(s)	Unknown	06-Dec-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEE0935467			Unknown	07-Dec-00	TEARING	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0935452		Second(s)	Unknown	07-Dec-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MC 0935473		Second(s)	Unknown	07-Dec-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAR0935724			Unknown	08-Dec-00	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRA0935690			Unknown	08-Dec-00	ALLERGIC REACTION	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CIA0935869		Second(s)	Unknown	11-Dec-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0935966	42	Year(s)	Female Adult	11-Dec-00	SWELLING	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0936443	72	Year(s)	Female Adult	14-Dec-00	IRRITATION	US	N	SKIN	2	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MUG0936360			Unknown	14-Dec-00	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0936687	43	Year(s)	Female Adult	18-Dec-00	REDNESS	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NIE0937263	78	Year(s)	Female Adult	21-Dec-00	TINGLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STR0937714		Second(s)	Unknown	27-Dec-00	REDNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEM0937660	63	Year(s)	Female Adult	27-Dec-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FLA0937912		Second(s)	Unknown	28-Dec-00	PEELING	US	N	SKIN	4	Day(s)

COMMENTS FOR CLEARASIL CLEARSTICK WITH SALICYLIC ACID

NA HEF Comments for [illegible]rsticks with Salicylic Acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	City	MD
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N
CLEARASIL CLEARSTICK SENS SKIN	TAN0716171	15	Year(s)	Female Child	03-Jan-97	RASH	US	N
CLEARSTICK MAX 1.2 OZ	MC 0716433		Unknown	Male Adult	06-Jan-97	RASH	US	N
CLEARSTICK MAX 1.2 OZ	TAN0716281	16	Year(s)	Male Child	06-Jan-97	RASH	US	N
CLEARSTICK MAX 1.2 OZ	OSO0716990		Unknown	Female Child	09-Jan-97	STINGING/BURNING	US	N
CLEARSTICK MAX 1.2 OZ	MC 0717711	12	Year(s)	Female Child	14-Jan-97	WARM	US	N
CLEARSTICK MAX 1.2 OZ	TRE0718445		Unknown	Female Child	21-Jan-97	PIMPLES	US	N
CLEARASIL CLEARSTICK SENS SKIN	HAY0719076	15	Year(s)	Female Child	23-Jan-97	WELTS	US	N
CLEARSTICK MAX 1.2 OZ	ROS0719022		Unknown	Female Adult	23-Jan-97	BURNING	US	N
CLEARASIL CLEARSTICK SENS SKIN	QUA0719250	14	Year(s)	Female Child	24-Jan-97	PEELING	US	N
CLEARASIL CLEARSTICK SENS SKIN	DEA0719726	22	Unknown	Male Adult	28-Jan-97	RASH	US	N
CLEARASIL CLEARSTICK ND	UNK0720546		Unknown	Female Adult	03-Feb-97	RASH	US	N
CLEARASIL CLEARSTICK SENS SKIN	OLS0721166	14	Year(s)	Female Adult	06-Feb-97	ACNE	US	N
CLEARSTICK MAX 1.2 OZ	ZEO0721169	13	Year(s)	Unknown	06-Feb-97	ACNE	US	N
CLEARASIL CLEARSTICK SENS SKIN	ARC0721373	65	Year(s)	Female Adult	07-Feb-97	BUMPS	US	N
CLEARSTICK MAX 1.2 OZ	PER0721812	14	Year(s)	Female Adult	11-Feb-97	REDNESS	US	N
CLEARASIL CLEARSTICK SENSITIVE ND	SHE0721960		Unknown	Female Adult	12-Feb-97	REDNESS	US	N
CLEARSTICK MAX 1.2 OZ	MIL0722204	13	Year(s)	Female Child	13-Feb-97	STINGING	US	N
CLEARSTICK MAX 1.2 OZ	SEE0722119	15	Year(s)	Unknown	13-Feb-97	PIMPLES	US	N
CLEARASIL CLEARSTICK ND	SCO0722857		Unknown	Female Child	20-Feb-97	DRYNESS	US	N
CLEARSTICK MAX 1.2 OZ	HAE0724355	11	Year(s)	Female Child	03-Mar-97	CUT	US	N
CLEARSTICK MAX 1.2 OZ	GRU0724679	14	Unknown	Unknown	05-Mar-97	BUMPS	US	N
CLEARASIL CLEARSTICK SENS SKIN	OHN0725046		Unknown	Male Adult	07-Mar-97	ACNE	US	N
CLEARSTICK MAX 1.2 OZ	WU0725368	12	Year(s)	Female Child	10-Mar-97	STINGING	US	N
CLEARSTICK MAX 1.2 OZ	NEW0725928	12	Year(s)	Female Child	13-Mar-97	RASH	US	N
CLEARASIL CLEARSTICK SENS SKIN	AAN0726619		Unknown	Female Adult	19-Mar-97	DRYNESS	US	N
CLEARASIL CLEARSTICK SENS SKIN	SAN0726812	14	Year(s)	Female Adult	19-Mar-97	REDNESS	US	N
CLEARASIL CLEARSTICK SENS SKIN	VAR0726699		Unknown	Female Child	19-Mar-97	ITCHING	US	N
CLEARASIL CLEARSTICK SENSITIVE ND	ROM0726807	14	Year(s)	Female Child	19-Mar-97	REDNESS	US	N
CLEARSTICK MAX 1.2 OZ	AAN0726618		Unknown	Female Adult	19-Mar-97	DRYNESS	US	N
CLEARSTICK MAX 1.2 OZ	RON0726729		Unknown	Female Child	19-Mar-97	REDNESS	US	N
CLEARASIL CLEARSTICK ND	WIL0727965		Unknown	Male Adult	27-Mar-97	PEELING	US	N
CLEARASIL CLEARSTICK SENS SKIN	SCH0727855	22	Year(s)	Male Adult	27-Mar-97	ITCHING	US	N
CLEARSTICK MAX 1.2 OZ	RAT0728379		Unknown	Male Adult	01-Apr-97	ACNE	US	N

DISC CLEARASIL CLEARSTICK MAXIMUM ND	MIL0728446	12	Year(s)	Female Child	01-Apr-97	DRYNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	STE0729399	15	Year(s)	Female Child	08-Apr-97	RASH	US	N	SKIN		Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MC 0729482		Unknown	Female Adult	09-Apr-97	ACNE	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	MAT0729623	13	Year(s)	Female Child	09-Apr-97	DRYNESS	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	SOT0729538	18	Year(s)	Female Adult	09-Apr-97	ACNE	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	IRB0729952	13	Year(s)	Female Child	11-Apr-97	BURNING	US	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	FRO0731665	14	Year(s)	Female Child	23-Apr-97	BURNING	US	N	SKIN	10	Minute(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	BAZ0731615		Unknown	Female Adult	23-Apr-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRO0732233		Unknown	Female Adult	28-Apr-97	DRYNESS	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	BRA0732395	12	Year(s)	Female Child	29-Apr-97	BLEMISHES	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	KOE0732360		Unknown	Female Adult	29-Apr-97	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	MOR0732547		Unknown	Female Child	30-Apr-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LIM0733433		Unknown	Female Adult	07-May-97	PEELING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	COS0733947	17	Year(s)	Female Child	12-May-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	SHA0733949		Unknown	Unknown	12-May-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	JAC0734019		Unknown	Male Adult	13-May-97	ACNE	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	WIL0734157		Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GOL0734598		Unknown	Female Adult	16-May-97	IRRITATION	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	OTT0734492	13	Year(s)	Female Child	16-May-97	BUMPS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	KUS0734626	12	Year(s)	Female Child	19-May-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	GRE0734983	14	Year(s)	Female Child	20-May-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	EYM0735145	12	Year(s)	Male Child	20-May-97	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	DAR0735284		Unknown	Male Child	21-May-97	TINGLING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	BAZ0735329	36	Year(s)	Female Adult	22-May-97	REDNESS	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	VIL0735636	14	Year(s)	Female Child	23-May-97	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	JOL0735760		Unknown	Male Adult	27-May-97	ITCHING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0736188	13	Year(s)	Female Child	29-May-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0736812	13	Year(s)	Female Child	03-Jun-97	BURNING	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	MCK0736983		Unknown	Female Adult	04-Jun-97	WELTS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	RIC0737357	21	Year(s)	Male Adult	06-Jun-97	REDNESS	US	N	SKIN	4	Unknown
CLEARSTICK MAX 1.2 OZ	ROL0737250	14	Year(s)	Female Child	06-Jun-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	ORR0737511	33	Year(s)	Female Adult	09-Jun-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	PAR0737922	14	Year(s)	Female Child	11-Jun-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	POR0737960	13	Year(s)	Female Child	11-Jun-97	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	GAR0737816	13	Unknown	Female Child	11-Jun-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	AWA0738323	14	Year(s)	Male Child	13-Jun-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRO0738624		Unknown	Female Child	17-Jun-97	BURNING	US	N	SKIN		

CLEARSTICK MAX 1.2 OZ	CAS0739906	34	Year(s)	Male Adult	25-Jun-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	HAY0740125		Unknown	Female Child	26-Jun-97	PEELING	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENSITIVE ND	SIM0740746	16	Year(s)	Male Child	01-Jul-97	CRAMPING	US	N	N		
CLEARSTICK MAX 1.2 OZ	BON0740674	12	Year(s)	Female Child	01-Jul-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	DEG0741377	11	Year(s)	Female Child	07-Jul-97	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	GOH0741512	15	Year(s)	Male Child	08-Jul-97	STINGING	US	N	SKIN	15	Minute(s)
CLEARSTICK MAX 1.2 OZ	FRE0741531	16	Unknown	Female Child	08-Jul-97	RASH	US	N	SKIN	6	Hour(s)
CLEARSTICK MAX 1.2 OZ	RAN0742322	13	Year(s)	Male Child	14-Jul-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	HAN0742441		Unknown	Female Child	15-Jul-97	PEELING	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	PAP0742717	15	Year(s)	Male Child	16-Jul-97	BURNING	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	REF0742745		Unknown	Female Child	16-Jul-97	BURNING	US	N	EYE		
CLEARASIL CLEARSTICK SENS SKIN	PER0742883	14	Year(s)	Female Child	17-Jul-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	VAN0742782	14	Year(s)	Female Child	17-Jul-97	OTHER	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	BOW0742816	14	Year(s)	Male Child	17-Jul-97	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MUR0742801	2	Year(s)	Female Child	17-Jul-97	NONE	US	N	N		
CLEARASIL CLEARSTICK SENS SKIN	GUE0742965	12	Year(s)	Female Child	18-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	HAN0743017	15	Year(s)	Female Adult	18-Jul-97	STINGING	US	N	SKIN	4	Minute(s)
CLEARSTICK MAX 1.2 OZ	PER0742976		Unknown	Female Adult	18-Jul-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	WIR0743219	19	Year(s)	Male Adult	21-Jul-97	IRRITATION	US	N	EYE	1	Hour(s)
CLEARASIL CLEARSTICK ND	BAN0744051		Unknown	Female Adult	25-Jul-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BLE0744792		Unknown	Female Child	31-Jul-97	PIMPLES	US	N	SKIN	1	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	PIE0745379	13	Year(s)	Female Child	04-Aug-97	ACNE	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SAN0745376		Unknown	Female Child	04-Aug-97	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	JON0745912	17	Unknown	Female Adult	07-Aug-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK ND	MAC0746588	19	Year(s)	Male Adult	12-Aug-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	UNK0747110		Unknown	Female Child	15-Aug-97	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BEL0747738	13	Year(s)	Unknown	20-Aug-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAR0747870	18	Year(s)	Female Adult	20-Aug-97	IRRITATION	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MON0749361		Unknown	Female Adult	02-Sep-97	RASH	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	MED0749873	15	Year(s)	Male Adult	03-Sep-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	RUS0750184	13	Year(s)	Female Adult	05-Sep-97	PEELING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	NGU0750564	13	Year(s)	Female Child	08-Sep-97	BUMPS	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	CHA0751179		Unknown	Unknown	11-Sep-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0751330	13	Year(s)	Unknown	12-Sep-97	DRYNESS	US	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	POR0751845	2	Year(s)	Male Child	16-Sep-97	NONE	CA	N	N		
CLR CST TRT REG ST NTNT 1.2 OZ	SAN0752493	41	Year(s)	Female Adult	19-Sep-97	DRYNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	KEN0753153	16	Year(s)	Female Child	23-Sep-97	BLISTERS	US	N	SKIN	1	Day(s)

CLEARSTICK MAX 1.2 OZ	MAR0753035	16	Year(s)	Female Child	23-Sep-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PRI0753414	19	Year(s)	Male Adult	24-Sep-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	LO 0753635	30	Year(s)	Female Adult	26-Sep-97	RASH	CA	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	OVE0754101	19	Year(s)	Female Adult	29-Sep-97	INFLAMED	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK ND	PER0755269	18	Year(s)	Male Adult	06-Oct-97	BLISTERS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	KLA0755012	13	Year(s)	Male Child	06-Oct-97	STINGING	CA	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	KON0755124	19	Year(s)	Female Adult	06-Oct-97	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	VEL0755501		Unknown	Male Child	07-Oct-97	RASH	US	N	SKIN		
CLEARASIL CLEARSTICK ND	REF0755792		Unknown	Female Adult	08-Oct-97	NONE	US	N	N		
CLEARASIL CLEARSTICK SENS SKIN	BRO0755759	12	Year(s)	Female Adult	08-Oct-97	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BEC0755762	14	Year(s)	Male Child	08-Oct-97	IRRITATION	US	N	EYE	2	Hour(s)
CLEARSTICK MAX 1.2 OZ	LIN0756742	13	Year(s)	Female Child	14-Oct-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RIO0756846		Unknown	Female Adult	15-Oct-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	SCO0758022	14	Year(s)	Female Child	21-Oct-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	DUB0758667	11	Year(s)	Female Child	24-Oct-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	RUS0759881	14	Year(s)	Female Child	31-Oct-97	IRRITATION	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	WIL0759917	17	Year(s)	Male Child	31-Oct-97	SORENESS	US	N	N	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	FEN0760495	12	Year(s)	Female Child	04-Nov-97	SWELLING	US	N	SKIN	12	Hour(s)
CLEARASIL CLEARSTICK SENS SKIN	UNK0761070	13	Year(s)	Female Child	07-Nov-97	PEELING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	JOH0761145		Unknown	Female Adult	07-Nov-97	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	LAN0761738	55	Year(s)	Male Adult	11-Nov-97	SWELLING	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	ROD0761788	15	Year(s)	Unknown	11-Nov-97	PIMPLES	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	REF0762261	13	Year(s)	Female Child	13-Nov-97	FLAKING	CA	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	WHE0762710	4	Year(s)	Male Child	17-Nov-97	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	RHY0763132	14	Year(s)	Female Child	18-Nov-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	COO0763391	15	Year(s)	Female Child	19-Nov-97	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	WIL0764090		Unknown	Male Adult	24-Nov-97	REDNESS	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	MC 0764409	11	Year(s)	Female Adult	25-Nov-97	REDNESS	US	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	CHA0765647	3	Year(s)	Male Child	03-Dec-97	SWELLING/INFLAMED	US	N	N		Unknown
CLEARSTICK MAX 1.2 OZ	GRI0766633	32	Year(s)	Female Adult	09-Dec-97	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	DAB0767560	13	Year(s)	Female Child	15-Dec-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	COL0769686	15	Unknown	Female Child	31-Dec-97	RASH	US	Y	SKIN		
CLEARSTICK MAX 1.2 OZ	BAR0770263	12	Year(s)	Unknown	05-Jan-98	BURNING	US	N	SKIN	5	Minute(s)
CLEARSTICK MAX 1.2 OZ	PAP0770852	16	Year(s)	Female Child	07-Jan-98	ACNE	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	PER0770814	16	Year(s)	Unknown	07-Jan-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	POP0770850		Unknown	Unknown	07-Jan-98	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	LIN0771069		Unknown	Female Adult	08-Jan-98	ACNE	US	N	SKIN		Unknown

CLEARSTICK MAX 1.2 OZ	PAP0771073	17	Year(s)	Female Child	08-Jan-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SPE0771062	14	Year(s)	Male Child	08-Jan-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	HOW0771332	12	Year(s)	Female Child	09-Jan-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	LOP0771903	15	Year(s)	Male Child	13-Jan-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	POP0772869	16	Year(s)	Female Adult	20-Jan-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	BAR0773638	15	Year(s)	Male Child	23-Jan-98	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GAR0773818	18	Year(s)	Female Adult	26-Jan-98	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	AHL0774230		Unknown	Male Adult	27-Jan-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	ZER0774827		Unknown	Unknown	29-Jan-98	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	MOS0775645	16	Year(s)	Female Adult	03-Feb-98	PIMPLES	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	DAV0776064		Unknown	Female Adult	06-Feb-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WON0776772		Unknown	Female Adult	10-Feb-98	IRRITATION	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RUI0777116	13	Year(s)	Female Child	11-Feb-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	BOW0777792	16	Year(s)	Female Child	17-Feb-98	RASH	US	N	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	WOO0777897	13	Year(s)	Female Child	17-Feb-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	FEE0778575		Unknown	Female Adult	20-Feb-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	NGU0779323		Unknown	Female Adult	25-Feb-98	PIMPLES	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK ND	SCH0779672	14	Year(s)	Female Child	26-Feb-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	COW0780097	53	Year(s)	Male Adult	02-Mar-98	REDNESS	US	N	SKIN	6	Hour(s)
CLEARSTICK MAX 1.2 OZ	VLA0780051		Unknown	Female Adult	02-Mar-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WOR0780188	13	Unknown	Female Adult	02-Mar-98	RASH	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	GOR0780756		Unknown	Unknown	04-Mar-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PER0780762		Unknown	Male Adult	04-Mar-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	NO 0781580		Unknown	Female Adult	09-Mar-98	RASH	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	HAY0782101	43	Year(s)	Female Adult	11-Mar-98	REDNESS	US	N	SKIN	2	Day(s)
CLR CST TRT REG ST NTNT 1.2 OZ	CAN0781879	20	Year(s)	Female Adult	11-Mar-98	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	VAR0783216		Unknown	Female Adult	17-Mar-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ALE0783574		Unknown	Female Adult	18-Mar-98	ACNE	US	Y	SKIN	2	Week(s)
CLEARASIL CLEARSTICK ND	THO0784407		Unknown	Unknown	23-Mar-98	IRRITATION	CA	N	SKIN	1	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	BER0784314	12	Year(s)	Female Child	23-Mar-98	STINGING	CA	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SAR0784894		Unknown	Male Adult	25-Mar-98	DISCOLORATION	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	LUC0786015	11	Year(s)	Female Child	01-Apr-98	STINGING	US	N	SKIN	5	Minute(s)
CLEARSTICK MAX 1.2 OZ	TIE0787306	13	Year(s)	Female Child	08-Apr-98	BUMPS	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	ORT0787743	15	Year(s)	Male Adult	13-Apr-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WHI0789964		Unknown	Female Adult	23-Apr-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FAR0790190	13	Year(s)	Male Child	24-Apr-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	TIE0790358	18	Year(s)	Female Adult	27-Apr-98	REDNESS	CA	N	SKIN	3	Week(s)

CLEARSTICK MAX 1.2 OZ	RAW0791661		Unknown	Male Adult	04-May-98	SWELLING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	WIL0791826	13	Year(s)	Male Child	04-May-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LAN0792032	38	Year(s)	Female Adult	05-May-98	REDNESS	CA	N	SKIN	4	Hour(s)
CLEARSTICK MAX 1.2 OZ	TES0792728	17	Year(s)	Male Child	08-May-98	ACNE	US	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	VED0792685		Unknown	Female Adult	08-May-98	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	TOR0793226	12	Year(s)	Female Adult	12-May-98	PEELING	US	Y	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	GUR0794679	30	Year(s)	Female Adult	21-May-98	ACNE	CA	N	SKIN	1	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	STE0794923	15	Year(s)	Female Child	25-May-98	REDNESS	CA	Y	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	ALI0795548	20	Year(s)	Female Adult	28-May-98	BURNING	CA	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GOO0796703	14	Year(s)	Male Child	04-Jun-98	RASH	US	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK ND	COL0796837	10	Year(s)	Unknown	05-Jun-98	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	HAM0797018	15	Year(s)	Female Adult	08-Jun-98	BUMPS	US	N	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	PRO0799252	33	Year(s)	Female Adult	22-Jun-98	BURNING	CA	N	SKIN	5	Minute(s)
CLEARASIL CLEARSTICK SENS SKIN	COU0800150	13	Unknown	Female Child	25-Jun-98	SWELLING	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	COU0801087	16	Year(s)	Female Child	01-Jul-98	RASH	US	N	SKIN	10	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GER0801540	12	Year(s)	Female Child	06-Jul-98	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	RHO0801722	13	Year(s)	Female Child	06-Jul-98	PIMPLES	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	NIC0801620	19	Unknown	Female Adult	06-Jul-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	OLL0802069	46	Year(s)	Female Adult	08-Jul-98	BURNING	CA	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAD0802120	13	Year(s)	Female Child	08-Jul-98	ACNE	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	SMI0802235	15	Year(s)	Female Child	08-Jul-98	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	HUD0802329		Unknown	Unknown	09-Jul-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	BUR0802792	15	Year(s)	Female Child	10-Jul-98	REDNESS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	ZOR0802730	14	Year(s)	Male Child	10-Jul-98	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	RIC0804385	12	Year(s)	Female Child	20-Jul-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SAX0804980	16	Year(s)	Female Child	22-Jul-98	RASH	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	BAR0805297	41	Year(s)	Female Adult	23-Jul-98	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	BEL0805143	37	Year(s)	Female Adult	23-Jul-98	ITCHING	US	N	SKIN	24	Hour(s)
CLEARSTICK MAX 1.2 OZ	MAD0805250	14	Year(s)	Unknown	23-Jul-98	STINGING	US	N	SKIN	1	Month(s)
CLR CST TRT REG ST NTNT 1.2 OZ	JAC0805077	24	Year(s)	Female Adult	23-Jul-98	BURNING	CA	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	BAR0805737	16	Year(s)	Female Child	27-Jul-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	MAL0805596		Unknown	Female Adult	27-Jul-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PEA0805965	12	Unknown	Female Child	27-Jul-98	BLEMISHES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	BRO0806709	17	Year(s)	Female Child	30-Jul-98	SWELLING	US	N	SKIN		Minute(s)
CLEARSTICK MAX 1.2 OZ	HAM0806966	16	Year(s)	Unknown	31-Jul-98	PIMPLES	US	N	SKIN	8	Day(s)
CLEARSTICK MAX 1.2 OZ	DAV0807131	13	Year(s)	Female Child	03-Aug-98	STINGING	US	N	SKIN	30	Second(s)
CLEARASIL CLEARSTICK ND	RAN0807700		Unknown	Female Adult	05-Aug-98	PIMPLES	CA	N	SKIN		Unknown

CLEARASIL CLEARSTICK SENS SKIN	JON0808077	38	Year(s)	Female Adult	06-Aug-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FRY0807912	21	Year(s)	Female Adult	06-Aug-98	STINGING	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	FLO0809194		Unknown	Male Adult	13-Aug-98	PEELING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	CIR0810457	19	Year(s)	Female Adult	19-Aug-98	(GENERALIZED)	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BIE0810376	15	Year(s)	Female Child	19-Aug-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAR0811564		Unknown	Female Adult	26-Aug-98	OTHER	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	PAR0811938	15	Year(s)	Male Child	28-Aug-98	BURNING	CA	N	SKIN	2	Minute(s)
CLEARSTICK MAX 1.2 OZ	BRI0811993		Unknown	Male Adult	28-Aug-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WAT0812364	13	Year(s)	Female Child	31-Aug-98	HIVES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	TRE0813001	21	Year(s)	Female Adult	03-Sep-98	BURNING	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	GRO0814533		Unknown	Female Adult	15-Sep-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	TRE0815223	13	Year(s)	Male Child	18-Sep-98	PEELING	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	HIR0816122		Unknown	Female Adult	25-Sep-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SIL0816637	15	Year(s)	Male Child	29-Sep-98	REDNESS	CA	Y	SKIN		
CLEARSTICK MAX 1.2 OZ	LA 0817607	12	Year(s)	Female Child	05-Oct-98	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PER0818014	15	Year(s)	Female Child	07-Oct-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SES0817984	18	Year(s)	Female Child	07-Oct-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	UNK0817996	18	Year(s)	Female Child	07-Oct-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK ND	NEL0818208		Unknown	Female Adult	08-Oct-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	KEN0819493	14	Year(s)	Unknown	16-Oct-98	RASH	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	KEM0820188	16	Year(s)	Male Child	21-Oct-98	BURNING	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	COR0822340	13	Year(s)	Male Adult	03-Nov-98	BLEEDING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0823329	33	Year(s)	Female Adult	09-Nov-98	ACNE	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	CAL0823537		Unknown	Female Adult	10-Nov-98	BURNING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	MAL0823490	22	Year(s)	Male Adult	10-Nov-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ODO0824817	13	Year(s)	Male Child	17-Nov-98	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SAN0826606	13	Year(s)	Female Adult	30-Nov-98	HIVES	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	REF0826432	35	Year(s)	Female Adult	30-Nov-98	REDNESS	CA	N	SKIN	3	007
CLEARSTICK MAX 1.2 OZ	REF0826432	35	Year(s)	Female Adult	30-Nov-98	REDNESS	CA	N	SKIN	3	007
CLEARSTICK MAX 1.2 OZ	BLA0826777	13	Unknown	Male Child	01-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	SCO0827018	20	Year(s)	Female Adult	02-Dec-98	PIMPLES	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	JON0828339		Unknown	Unknown	10-Dec-98	SWELLING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	YOS0828693	16	Year(s)	Female Child	14-Dec-98	TEARING	US	N	EYE	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	VIT0830142	14	Year(s)	Female Child	22-Dec-98	REDNESS	US	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	BEL0830947		Unknown	Male Child	30-Dec-98	STINGING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	SMI0831054	23	Year(s)	Female Adult	30-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	DUJ0835784	14	Year(s)	Female Child	28-Jan-99	ACNE	CA	N	SKIN	2	Day(s)

CLEARSTICK MAX 1.2 OZ	SHU0839052	15	Year(s)	Male Adult	17-Feb-99	PIMPLES	US	N	SKIN		Day(s)
CLEARSTICK MAX 1.2 OZ	JEW0839147		Unknown	Female Adult	18-Feb-99	REDNESS	US	N	SKIN		
DISC CLEARASIL CLEARSTICK MAXIMUM ND	GAR0839854	13	Year(s)	Female Child	22-Feb-99	STINGING	US	N	SKIN	3	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	KIN0840890	15	Year(s)	Female Adult	26-Feb-99	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MOR0841993		Unknown	Female Adult	04-Mar-99	SWELLING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	LOG0842310	13	Year(s)	Female Child	05-Mar-99	REDNESS	US	N	SKIN	7	Hour(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	EDW0842168		Unknown	Female Adult	05-Mar-99	BURNING	US	N	SKIN	2	Minute(s)
CLEARSTICK MAX 1.2 OZ	HER0842737	33	Year(s)	Female Adult	08-Mar-99	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	REF0843654		Unknown	Unknown	12-Mar-99	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	WOL0845747		Unknown	Male Adult	23-Mar-99	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RUB0847541		Unknown	Male Adult	01-Apr-99	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MET0848570	19	Year(s)	Female Adult	08-Apr-99	BURNING	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	SEC0849152	10	Year(s)	Male Child	12-Apr-99	SWELLING	US	N	SKIN	5	Day(s)
CLR CST TRT REG ST NTNT 1.2 OZ	SIC0849127	11	Year(s)	Male Child	12-Apr-99	RASH	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MIC0849363		Unknown	Female Adult	13-Apr-99	SORENESS	US	N	SKIN	1	Day(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	AND0850573		Unknown	Male Adult	19-Apr-99	BURNING	US	N	SKIN	1	Week(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	GUD0850586	13	Year(s)	Male Child	19-Apr-99	ITCHING	US	N	SKIN	4	Day(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	BAN0851561	2	Year(s)	Male Child	26-Apr-99	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	YAN0852146		Unknown	Unknown	28-Apr-99	ITCHING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	SAN0852968	16	Year(s)	Female Adult	03-May-99	DISCOLORATION	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	SUA0854488	13	Year(s)	Male Child	11-May-99	PEELING	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	UNK0854344		Unknown	Female Child	11-May-99	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	MAX0855686		Unknown	Female Child	18-May-99	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ADA0856898		Unknown	Female Adult	25-May-99	PIMPLES	US	Y	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	CAR0856906	16	Year(s)	Male Child	25-May-99	SWELLING	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	CRU0858768		Unknown	Male Adult	04-Jun-99	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK ND	GON0859031		Unknown	Unknown	07-Jun-99	PIMPLES	US	N	SKIN	3	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	LUC0859971	29	Year(s)	Male Adult	14-Jun-99	PIMPLES	CA	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	REF0864575		Unknown	Male Adult	12-Jul-99	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FES0864728	15	Year(s)	Female Child	13-Jul-99	BURNING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	HIC0864779	18	Year(s)	Female Adult	13-Jul-99	BUMPS	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	MCA0866143	14	Year(s)	Female Adult	21-Jul-99	RASH	CA	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LAW0866728	12	Year(s)	Female Child	26-Jul-99	ACNE	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	COL0871107	13	Year(s)	Female Child	24-Aug-99	ACNE	US	Y	SKIN		
CLEARASIL CLEARSTICK ND	DAV0871883	15	Year(s)	Male Child	30-Aug-99	BURNING	US	N	SKIN	4	Minute(s)
CLEARSTICK MAX 1.2 OZ	HAS0873537	21	Year(s)	Male Adult	09-Sep-99	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BUT0873739	25	Year(s)	Female Child	10-Sep-99	PIMPLES	US	N	SKIN	2	Day(s)

CLEARSTICK MAX 1.2 OZ	SMI0876377		Unknown	Unknown	28-Sep-99	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ADE0876885		Unknown	Female Adult	01-Oct-99	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BAK0877485	27	Year(s)	Female Adult	06-Oct-99	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	SCO0883283		Unknown	Female Adult	12-Nov-99	DRYNESS	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	SCO0883282		Unknown	Female Adult	12-Nov-99	DRYNESS	US	N	SKIN	3	Week(s)
CLEARASIL CLEARSTICK ND	YAN0883847	30	Year(s)	Female Adult	16-Nov-99	REDNESS	CA	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK REGULAR ND	GAR0885111		Unknown	Female Adult	26-Nov-99	RASH	CA	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	EGA0895244	13	Year(s)	Male Child	09-Feb-00	DISCOLORATION	CA	N	SKIN	8	Hour(s)
CLEARASIL CLEARSTICK ND	POO0895856	16	Year(s)	Male Child	14-Feb-00	IRRITATION	CA	N	EYE	5	Minute(s)
CLEARASIL CLEARSTICK ND	DEA0897856		Unknown	Female Adult	28-Feb-00	RASH	US	N	SKIN	36	Hour(s)
CLR CST TRT REG ST NTNT 1.2 OZ	BAR0901284		Unknown	Female Child	21-Mar-00	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	KAU0901929	20	Year(s)	Female Adult	27-Mar-00	BURNING	CA	N	SKIN	5	Minute(s)
CLEARASIL CLEARSTICK ND	UNK0905799		Unknown	Unknown	24-Apr-00	BUMPS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SCO0909301	15	Year(s)	Female Child	19-May-00	RASH	US	N	SKIN	3	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	GAL0911185	32	Year(s)	Female Adult	05-Jun-00	REDNESS	CA	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	KES0911397	20	Unknown	Female Adult	05-Jun-00	RASH	US	N	SKIN	8	Hour(s)
CLEARSTICK MAX 1.2 OZ	FAT0911578		Unknown	Unknown	06-Jun-00	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	OSE0913983	17	Year(s)	Female Child	27-Jun-00	REDNESS	CA	N	SKIN	5	Minute(s)
DISCONTINUED CLEARASIL CLEARSTICK ND	LAW0915839	13	Year(s)	Female Child	17-Jul-00	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRY0915982	13	Year(s)	Female Child	18-Jul-00	HEADACHE	US	N	ON		
CLEARASIL CLEARSTICK ND	HAR0919844			Unknown	21-Aug-00	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MOR0920527	50	Year(s)	Female Adult	25-Aug-00	SWELLING	US	Y	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	SPE0922435			Unknown	11-Sep-00	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	FAU0925172	14	Year(s)	Male Child	29-Sep-00	IRRITATION	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	WIL0933771			Unknown	22-Nov-00	BURNING	US	N	SKIN		
DISC CLEARASIL CLEARSTICK MAXIMUM ND	ALL0934803	24	Year(s)	Female Adult	01-Dec-00	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK ND	FLO0935435	16	Year(s)	Female Child	06-Dec-00	BURNING	US	N	EYE		
CLEARASIL CLEARSTICK SENS SKIN	BOL0935938			Unknown	11-Dec-00	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	SAR0936080			Unknown	12-Dec-00	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	PIZ0937262			Unknown	21-Dec-00	PIMPLES	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	ST 0937386			Unknown	21-Dec-00	STINGING	CA	N	SKIN		

CMMENTS FOR CLEARASIL PADS WITH SALICYLIC ACID

NA HEF Comments for C[illegible]asil Pads with Salicylic Acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Ctry	MD	Incident	Duration	Amount
CLEARASIL PADS MAXIMUM 50 COUNT	HOG0716703		Unknown	Female Adult	08-Jan-97	RASH	US	N	SKIN	2	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MAC0716760		Unknown	Female Child	08-Jan-97	BUMPS	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	FRY0717037	16	Year(s)	Male Adult	09-Jan-97	STINGING/BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KIV0717273	14	Year(s)	Male Adult	13-Jan-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SMI0717330		Unknown	Female Adult	13-Jan-97	CRACKING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	JOS0717856		Unknown	Female Adult	15-Jan-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OLS0718326	18	Year(s)	Female Adult	17-Jan-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TOR0718591	12	Year(s)	Female Child	21-Jan-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	FIG0718654	15	Year(s)	Female Child	22-Jan-97	SORENESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KEL0718813	12	Year(s)	Female Child	22-Jan-97	RASH	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JOH0719222	15	Year(s)	Male Adult	24-Jan-97	PIMPLES	US	N	SKIN	3	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	COL0719665		Unknown	Male Child	28-Jan-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	OSB0719837		Unknown	Female Adult	29-Jan-97	BUMPS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ARN0720107	14	Unknown	Male Adult	30-Jan-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KAN0720388	17	Year(s)	Female Child	31-Jan-97	BUMPS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NUD0720336		Unknown	Male Adult	31-Jan-97	ACNE	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	TOL0720544	31	Year(s)	Female Adult	03-Feb-97	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	HIR0721043	16	Year(s)	Female Child	05-Feb-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	TOR0720967	14	Year(s)	Female Child	05-Feb-97	ITCHING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	DIS0721325	13	Year(s)	Female Child	07-Feb-97	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	CAR0721578		Unknown	Female Child	10-Feb-97	PIMPLES	US	N	SKIN	6	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEN0721535	21	Year(s)	Female Adult	10-Feb-97	REDNESS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NEA0721621	11	Year(s)	Female Child	10-Feb-97	BUMPS	US	N	SKIN	5	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SAB0721585	13	Year(s)	Female Child	10-Feb-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ADA0722193		Unknown	Female Adult	13-Feb-97	PIMPLES	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	AQT0722122	18	Year(s)	Female Adult	13-Feb-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	GON0722164	12	Year(s)	Female Child	13-Feb-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MOR0722201		Unknown	Female Child	13-Feb-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ORT0722964	12	Year(s)	Female Child	20-Feb-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	REY0723203	24	Year(s)	Female Adult	21-Feb-97	BUMPS	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	HOO0723878	16	Year(s)	Female Child	26-Feb-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MC 0724025	17	Year(s)	Male Adult	27-Feb-97	PIMPLES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	COL0724117	18	Year(s)	Unknown	28-Feb-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KIL0724410	25	Year(s)	Male Adult	03-Mar-97	BURNING	US	N	SKIN	20	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LA 0725157	13	Year(s)	Female Child	10-Mar-97	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ESA0725947		Unknown	Female Adult	14-Mar-97	BLISTERS	US	N	SKIN		

CLEARASIL PADS MAXIMUM 50 COUNT	ADA0726559	14	Year(s)	Male Adult	18-Mar-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OAK0726809	27	Year(s)	Female Adult	19-Mar-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	FAR0726748		Unknown	Male Adult	19-Mar-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	HAL0726918	15	Year(s)	Unknown	20-Mar-97	RASH	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JON0727639	13	Year(s)	Male Child	25-Mar-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NIB0727743	13	Year(s)	Male Child	26-Mar-97	SCRATCH	US	N	INJURY		
CLEARASIL PADS MAXIMUM 50 COUNT	GIL0728258	12	Year(s)	Male Child	31-Mar-97	RASH	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DAR0728278	14	Year(s)	Male Child	01-Apr-97	ACNE	US	N	SKIN	3	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JEW0729210		Unknown	Female Child	07-Apr-97	REDNESS	US	N	SKIN	8	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KAH0729311	16	Year(s)	Unknown	08-Apr-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAX NTNT 40 COUNT	ADA0729794		Unknown	Female Adult	10-Apr-97	PIMPLES	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	FIN0729675	13	Year(s)	Unknown	10-Apr-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAT0729710		Unknown	Female Adult	10-Apr-97	IRRITATION	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KOE0730444	12	Year(s)	Unknown	15-Apr-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAN0730392	15	Year(s)	Female Child	15-Apr-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LIE0730611	12	Year(s)	Female Child	16-Apr-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	BOO0730991	15	Year(s)	Female Child	18-Apr-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEE0731142		Unknown	Female Adult	21-Apr-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TRE0731254	22	Year(s)	Female Adult	21-Apr-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MOG0731409	15	Unknown	Male Child	22-Apr-97	DRYNESS	US	N	SKIN	4	Week(s)
CLEARASIL PADS ND	REF0732554		Unknown	Female Child	30-Apr-97	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	RIE0733129	12	Year(s)	Female Child	05-May-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	PHO0733303	14	Year(s)	Female Child	06-May-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BRA0734108	16	Year(s)	Male Adult	13-May-97	RASH	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BUR0734184	11	Year(s)	Male Child	13-May-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SAN0734089		Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	6	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	HOR0734552	21	Year(s)	Male Adult	16-May-97	BUMPS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	GUT0734608	16	Year(s)	Female Child	16-May-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	UNK0734555		Unknown	Unknown	16-May-97	REDNESS	US	N	EYE	5	Minute(s)
CLEARASIL PADS ND	WEL0734407		Unknown	Female Adult	16-May-97	DRYNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OZA0734906		Unknown	Female Adult	19-May-97	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KOS0735614	12	Year(s)	Unknown	23-May-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	COO0736065	15	Year(s)	Female Child	28-May-97	DISCOLORATION	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEL0735974	41	Year(s)	Male Adult	28-May-97	RUNNY NOSE	US	N	ON		
CLEARASIL PADS MAXIMUM 50 COUNT	BOS0736265	16	Year(s)	Male Child	29-May-97	PIMPLES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	UNG0736224		Unknown	Female Child	29-May-97	STINGING	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BLA0736431	27	Year(s)	Female Adult	30-May-97	RASH	US	N	SKIN	1	Day(s)

CLEARASIL PADS MAXIMUM 50 COUNT	STE0736535	13	Year(s)	Male Child	02-Jun-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS ND	PER0736549		Unknown	Female Adult	02-Jun-97	BLISTERS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WUN0737164	15	Year(s)	Female Child	05-Jun-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	JAV0737721		Unknown	Male Adult	10-Jun-97	ACNE	US	N	SKIN	2	006
CLEARASIL PADS MAXIMUM 50 COUNT	MC 0737767	13	Year(s)	Male Adult	10-Jun-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	REF0737727	13	Unknown	Female Adult	10-Jun-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	LEE0737625	16	Year(s)	Male Child	10-Jun-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	PAU0737974	18	Year(s)	Female Adult	11-Jun-97	BURNING	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	SAN0737814	17	Year(s)	Male Child	11-Jun-97	PEELING	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WUT0738324		Unknown	Female Adult	13-Jun-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	ALT0738525	13	Year(s)	Male Child	16-Jun-97	SWELLING	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LYN0738547		Unknown	Female Adult	16-Jun-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WES0738478	15	Unknown	Female Child	16-Jun-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	RIC0739093		Unknown	Male Child	19-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TRA0739013	13	Year(s)	Female Child	19-Jun-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MAT0739301	16	Year(s)	Female Child	23-Jun-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MOY0739739	17	Year(s)	Male Adult	24-Jun-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WAD0739934	17	Year(s)	Female Child	25-Jun-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	PIE0740077		Unknown	Female Child	26-Jun-97	RASH	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KUL0740199		Unknown	Male Child	27-Jun-97	ACNE	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BES0740685		Unknown	Female Adult	01-Jul-97	BLISTERS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JOH0740696		Unknown	Female Child	01-Jul-97	PIMPLES	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	HEI0740851	13	Year(s)	Female Child	02-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MAR0741488	13	Year(s)	Male Adult	08-Jul-97	RASH	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	HOU0741746		Unknown	Unknown	09-Jul-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KEA0741796	28	Year(s)	Male Adult	09-Jul-97	SORES	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ROB0741767		Unknown	Female Child	09-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	DIL0742230	53	Year(s)	Female Adult	14-Jul-97	HEADACHE	US	N	SKIN	20	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BOW0742818	14	Year(s)	Male Child	17-Jul-97	RASH	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WAD0742862	16	Year(s)	Male Child	17-Jul-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ZIN0743303	13	Year(s)	Female Child	21-Jul-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	LAC0743521		Unknown	Female Adult	22-Jul-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JET0743681	15	Year(s)	Female Child	23-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS ND	LOP0744201		Unknown	Female Child	28-Jul-97	RASH	US	N	SKIN		
CLEARASIL PADS REG NTNT 40 COUNT	KAT0744715		Unknown	Male Adult	30-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BEC0745010	15	Year(s)	Female Child	01-Aug-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WHA0745334	12	Year(s)	Female Child	04-Aug-97	BUMPS	US	N	SKIN	1	Day(s)

DISC CLEARASIL PADS REGULAR STRENGTH ND	SAI0745190	18	Year(s)	Male Adult	04-Aug-97	REDNESS	US	N	SKIN	6	Day(s)
CLEARASIL PADS ND	GIL0745550	14	Year(s)	Female Adult	05-Aug-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WAL0746118	7	Year(s)	Female Child	08-Aug-97	REDNESS	US	N	SKIN	8	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DAR0746295	16	Year(s)	Male Child	11-Aug-97	PEELING	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	UNK0746263		Unknown	Male Adult	11-Aug-97	PEELING	US	N	SKIN	2	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	JAM0746889	25	Year(s)	Male Adult	14-Aug-97	ACNE	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAS0747474	40	Year(s)	Female Adult	19-Aug-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	CAR0748542	14	Year(s)	Female Child	25-Aug-97	WELTS	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	PAL0749297	14	Year(s)	Female Child	29-Aug-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	HOU0749794		Unknown	Male Adult	03-Sep-97	PEELING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	STR0750496	15	Year(s)	Female Child	08-Sep-97	SCRATCH	US	N	INJURY	3	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	ISA0751819		Unknown	Female Child	16-Sep-97	PEELING	US	N	SKIN	1	006
CLEARASIL PADS ND	SCA0753814	14	Year(s)	Female Child	26-Sep-97	BUMPS	US	N	SKIN		
CLEARASIL PADS ND	PRE0753995	15	Year(s)	Male Child	29-Sep-97	ACNE	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LED0754845	18	Year(s)	Female Adult	03-Oct-97	ACNE	US	N	SKIN	11	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WRI0755606	13	Year(s)	Male Child	08-Oct-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS ND	SEU0756220	12	Year(s)	Female Child	10-Oct-97	RASH	US	N	SKIN		
CLEARASIL PADS ND	REC0756430	13	Year(s)	Female Child	13-Oct-97	IRRITATION	US	N	SKIN	4	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BER0757666		Unknown	Female Adult	20-Oct-97	SORES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SHA0758902	12	Year(s)	Female Child	27-Oct-97	REDNESS	US	N	EYE	20	Hour(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	CAR0759462	13	Year(s)	Male Child	29-Oct-97	RASH	CA	N	SKIN	2	Week(s)
CLEARASIL PADS ND	ZAB0760896		Unknown	Male Adult	06-Nov-97	SORES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	RUS0761178	13	Year(s)	Female Child	07-Nov-97	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	KEL0761465		Unknown	Male Adult	10-Nov-97	RASH	US	N	SKIN		
CLEARASIL PADS ND	REE0763110	14	Year(s)	Female Child	18-Nov-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BOB0763556		Unknown	Unknown	20-Nov-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KEN0773159	12	Year(s)	Male Child	21-Jan-98	RASH	US	N	SKIN		
CLEARASIL PADS ND	POG0773314		Unknown	Female Adult	22-Jan-98	ACNE	US	N	SKIN	3	Day(s)
CLR PADS REG 65 CT	RIC0773877	13	Year(s)	Female Child	26-Jan-98	REDNESS	CA	N	SKIN	12	Hour(s)
CLEARASIL PADS REG NTNT 40 COUNT	DIN0774705	15	Year(s)	Female Child	29-Jan-98	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	MUR0775061	15	Year(s)	Female Adult	30-Jan-98	STINGING	US	N	SKIN		
CLEARASIL PADS REG NTNT 40 COUNT	FEA0774951		Unknown	Unknown	30-Jan-98	STINGING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	EVA0775248	16	Year(s)	Female Child	02-Feb-98	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	AVI0775588	14	Unknown	Female Adult	03-Feb-98	ACNE	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	FRA0775825		Unknown	Female Adult	04-Feb-98	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	AL-0777041		Unknown	Female Adult	11-Feb-98	BUMPS	US	N	SKIN		
CLEARASIL PADS ND	QUI0777120		Unknown	Female Child	11-Feb-98	BURNING	US	N	SKIN		

CLEARASIL PADS MAXIMUM 50 COUNT	ELK0779011	17	Year(s)	Female Child	24-Feb-98	RASH	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	MED0779619		Unknown	Unknown	26-Feb-98	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	KAM0781053		Unknown	Unknown	06-Mar-98	BUMPS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ROM0782148	16	Year(s)	Male Child	12-Mar-98	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	VAR0782421		Unknown	Female Adult	13-Mar-98	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	FRY0783129		Unknown	Unknown	17-Mar-98	ACNE	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	WIL0787193	14	Year(s)	Male Adult	08-Apr-98	DRYNESS	US	N	SKIN	1	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	PAL0787524	12	Year(s)	Female Child	09-Apr-98	STINGING	US	N	SKIN		
CLEARASIL PADS ND	FIE0788176	14	Year(s)	Male Child	14-Apr-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	SAC0789133	15	Year(s)	Female Child	20-Apr-98	FLUSHED	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	SMI0790208		Unknown	Unknown	24-Apr-98	BUMPS	US	N	SKIN	5	Minute(s)
CLEARASIL PADS ND	CAS0794321	15	Year(s)	Male Child	19-May-98	PEELING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	LEE0796568	14	Year(s)	Female Child	03-Jun-98	RASH	US	N	SKIN	10	Minute(s)
CLR PADS REG 65 CT	X0798235	0	Unknown	Unknown	15-Jun-98	NONE	CA	N	SKIN		
CLEARASIL PADS ND	FLA0801495		Unknown	Female Adult	06-Jul-98	SCRATCH	US	N	SKIN		
CLEARASIL PADS ND	EDW0804435	19	Year(s)	Male Adult	20-Jul-98	SWELLING	US	N	SKIN	40	Minute(s)
CLEARASIL PADS ND	ANG0805062	21	Year(s)	Female Adult	22-Jul-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	JON0808076	13	Year(s)	Male Child	06-Aug-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	JON0808076	38	Year(s)	Female Adult	06-Aug-98	BURNING	US	N	SKIN	3	Week(s)
CLR PADS REG 65 CT	KOS0807830	16	Year(s)	Male Child	06-Aug-98	PIMPLES	CA	N	SKIN	1	006
CLEARASIL PADS ND	CUR0809365	14	Year(s)	Female Child	13-Aug-98	PIMPLES	CA	N	SKIN	3	Day(s)
CLR PADS REG 65 CT	KRU0809611	15	Year(s)	Male Child	14-Aug-98	ITCHING	CA	N	SKIN		
CLEARASIL PADS ND	BOB0810486		Unknown	Female Adult	20-Aug-98	DRYNESS	US	N	SKIN		Hour(s)
CLEARASIL PADS ND	REF0812055		Unknown	Female Child	28-Aug-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	ZAR0812073		Unknown	Female Child	28-Aug-98	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	BOR0812248	11	Year(s)	Female Child	31-Aug-98	REDNESS	US	N	SKIN	7	Hour(s)
CLR PADS REG 65 CT	GIF0812494	19	Year(s)	Male Adult	01-Sep-98	REDNESS	CA	N	SKIN	1	Week(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	MON0812390	16	Year(s)	Female Child	01-Sep-98	RASH	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	CAN0813066	13	Year(s)	Male Child	03-Sep-98	ACNE	US	N	SKIN	2	Week(s)
CLEARASIL PADS REG NTNT 40 COUNT	SAN0816101	14	Year(s)	Male Child	24-Sep-98	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	CAR0822440	14	Year(s)	Male Child	04-Nov-98	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	FUL0827932	14	Year(s)	Female Child	08-Dec-98	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS ND	IRE0828843	2	Year(s)	Female Child	14-Dec-98	NONE	US	N	N		
CLEARASIL PADS ND	WIE0829058	13	Year(s)	Male Child	15-Dec-98	IRRITATION	US	N	EYE	2	Day(s)
CLEARASIL PADS ND	SOT0829666	20	Year(s)	Female Adult	18-Dec-98	REDNESS	US	N	SKIN	24	Hour(s)
CLEARASIL PADS ND	STA0831761		Unknown	Unknown	05-Jan-99	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	REF0832174	20	Year(s)	Male Adult	07-Jan-99	SWELLING	US	N	SKIN	10	Minute(s)

CLEARASIL PADS ND	HEA0835056	16	Year(s)	Female Adult	25-Jan-99	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	DEL0836809	38	Year(s)	Female Adult	03-Feb-99	BURNING	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	LOP0836652	13	Year(s)	Male Adult	03-Feb-99	STINGING	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	THO0838996	13	Year(s)	Female Child	17-Feb-99	BURNING	US	N	SKIN		
CLEARASIL PADS ND	MOR0839859	13	Year(s)	Female Child	22-Feb-99	STINGING	US	N	SKIN	30	Minute(s)
CLEARASIL PADS ND	SIM0839868	17	Year(s)	Male Adult	22-Feb-99	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	CAS0844117	15	Year(s)	Male Child	15-Mar-99	RASH	US	N	SKIN	3	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	GRI0855323	39	Year(s)	Male Adult	17-May-99	SWELLING	US	N	SKIN	9	Hour(s)
CLEARASIL PADS ND	DIX0858976	13	Year(s)	Male Child	07-Jun-99	PEELING	US	N	SKIN		Unknown
CLR PADS REG 65 CT	CHI0861753	23	Year(s)	Male Adult	23-Jun-99	SCRATCH	CA	N	SKIN	1	Day(s)
CLR PADS REG 65 CT	HAI0865306	18	Year(s)	Female Adult	16-Jul-99	CUT, SCRATCH	CA	N	SKIN	3	Day(s)
CLEARASIL PADS ND	REF0867741	15	Year(s)	Female Adult	02-Aug-99	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS ND	LAR0870286		Unknown	Unknown	19-Aug-99	ACNE	US	N	SKIN		
CLEARASIL PADS ND	ALL0872950	17	Year(s)	Male Adult	07-Sep-99	PIMPLES	US	N	SKIN	1	Week(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	KRA0873972	17	Year(s)	Female Adult	13-Sep-99	ACNE	US	N	SKIN	3	Week(s)
CLEARASIL PADS ND	WIL0874791		Unknown	Male Adult	18-Sep-99	REDNESS	US	N	SKIN		
CLR PADS REG 65 CT	HOW0874918	14	Year(s)	Male Child	20-Sep-99	NONE	CA	N	N		
CLR PADS REG 65 CT	LEB0878042	14	Year(s)	Female Child	08-Oct-99	ITCHING	CA	N	SKIN	2	Day(s)
CLEARASIL PADS ND	JAC0878274	24	Year(s)	Unknown	11-Oct-99	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	BON0879569	1	Year(s)	Male Child	19-Oct-99	NONE	US	N	N		
CLEARASIL PADS ND	HOU0882550	18	Year(s)	Male Adult	08-Nov-99	RASH	CA	N	SKIN		
CLEARASIL PADS ND	KIN0884532	18	Year(s)	Female Adult	22-Nov-99	NONE	US	N	N		
CLR PADS REG 65 CT	KER0884445	10	Year(s)	Female Child	22-Nov-99	REDNESS	CA	N	SKIN		
CLEARASIL PADS ND	LUF0885868		Unknown	Unknown	02-Dec-99	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	MAR0889410	16	Year(s)	Female Child	30-Dec-99	RASH	US	N	SKIN	3	006
CLR PADS REG 65 CT	GAL0890565	15	Year(s)	Female Child	10-Jan-00	REDNESS	CA	N	SKIN	1	Week(s)
CLEARASIL PADS ND	HAU0897726		Unknown	Female Adult	26-Feb-00	IRRITATION	US	N	SKIN		
CLEARASIL PADS ND	JOH0900113	20	Year(s)	Female Adult	13-Mar-00	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	HOO0901038		Unknown	Unknown	20-Mar-00	BUMPS	US	N	SKIN	5	Day(s)
CLEARASIL PADS ND	AND0903662		Unknown	Unknown	06-Apr-00	BURNING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	PON0908393	40	Year(s)	Female Adult	12-May-00	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	MIL0915098	25	Year(s)	Male Adult	10-Jul-00	REDNESS	CA	N	SKIN		
CLEARASIL PADS ND	ELS0915471			Unknown	13-Jul-00	DRYNESS	US	N	SKIN	1	Week(s)
CLR PADS REG 65 CT	ZOT0915940	14	Year(s)	Male Child	18-Jul-00	REDNESS	CA	N	SKIN	1	Week(s)
CLEARASIL PADS ND	REF0917598			Unknown	31-Jul-00	BURNING	US	N	EYE		
CLEARASIL PADS ND	RYA0917374			Female Adult	31-Jul-00	SWELLING	US	N	SKIN		
CLEARASIL PADS ND	SAU0922538			Unknown	12-Sep-00	BURNING	US	N	SKIN		

NA HEF Comm... for Clearasil Pads
1997-2000

CLEARASIL PADS ND	FOX0923678			Unknown	20-Sep-00	SCRATCH	US	N	SKIN		
CLEARASIL PADS ND	MIL0927666	22	Year(s)	Female Adult	16-Oct-00	BURNING	US	N	SKIN		
CLEARASIL PADS ND	HEN0928814				23-Oct-00	PIMPLES	US	N	SKIN		
CLEARASIL PADS ND	EST0929087			Unknown	25-Oct-00	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	CHA0931094	30	Year(s)	Female Adult	06-Nov-00	BURNING	US	N	SKIN		
CLR PADS REG 65 CT	FLA0935191	31	Year(s)	Female Adult	05-Dec-00	SCRATCH	CA	N	SKIN		
CLEARASIL PADS ND	KHO0936092			Unknown	12-Dec-00	REDNESS	US	N	SKIN		

COMMENTS FOR NOXEMA PRODUCTS CONTAINING SALICYLIC ACID

NA HEF Comments for NOXZE products containing salicylic acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Cty
NOX ORI PAD REG PAD NTNT 50 CT	BER0715899		Unknown	Male Adult	02-Jan-97	DRYNESS	US
NOX ORI PAD REG PAD NTNT 50 CT	ALM0716299		Unknown	Female Child	06-Jan-97	SCRATCH	US
NOXZEMA PADS MAXIMUM STRENGTH ND	SAQ0716449		Unknown	Female Adult	06-Jan-97	ACNE	US
NOX ASPTC ASTR XTR 8 OZ	YAN0716674	23	Year(s)	Female Adult	07-Jan-97	REDNESS	US
NOXZEMA PADS MAXIMUM STRENGTH ND	BOW0716678	13	Year(s)	Female Child	07-Jan-97	RASH	US
NOXZEMA PADS MAXIMUM STRENGTH ND	EVA0716615	35	Year(s)	Female Adult	07-Jan-97	SWELLING/INFLAMED	US
NOXZEMA PADS MAXIMUM STRENGTH ND	MAS0716665		Unknown	Female Child	07-Jan-97	DRYNESS	US
NOXZEMA PADS MAXIMUM STRENGTH ND	REE0716500		Unknown	Female Adult	07-Jan-97	CUT, SCRATCH	US
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0716569	14	Year(s)	Female Child	07-Jan-97	ITCHING	US
NOX ASPTC ASTR XTR 8 OZ	COO0716814	14	Year(s)	Female Child	08-Jan-97	SWELLING/INFLAMED	US
NOX ORI PAD REG PAD NTNT 50 CT	MED0716879	14	Year(s)	Male Child	08-Jan-97	PIMPLES	US
NOX ORI PAD MAX PAD NTNT 50 CT	FUN0717050		Unknown	Male Adult	09-Jan-97	REDNESS	US
NOX ORI PAD MAX PAD NTNT 50 CT	BLU0717166	14	Year(s)	Unknown	10-Jan-97	ACNE	US
NOX ORI PAD MAX PAD NTNT 50 CT	FLO0717496		Unknown	Female Adult	13-Jan-97	RASH	US
NOX ORI PAD REG PAD NTNT 50 CT	BOR0717460		Unknown	Female Adult	13-Jan-97	REDNESS	US
NOX ORI PAD REG PAD NTNT 50 CT	GAR0717504	14	Year(s)	Male Adult	13-Jan-97	BUMPS	US
NOXZEMA PADS MAXIMUM STRENGTH ND	WHA0717457	10	Year(s)	Female Child	13-Jan-97	PIMPLES	US
NOX ORI PAD MAX PAD NTNT 50 CT	CUC0717736	12	Year(s)	Female Child	14-Jan-97	DRYNESS	US
NOX ORI PAD MAX PAD NTNT 50 CT	FAT0717746	11	Year(s)	Female Child	14-Jan-97	STINGING	US
NOX ASPTC ASTR XTR 8 OZ	CLA0717927	14	Year(s)	Female Child	15-Jan-97	ACNE	US
NOXZEMA PADS MAXIMUM STRENGTH ND	GIB0717798		Unknown	Female Adult	15-Jan-97	BURNING	US
NOX ORI PAD REG PAD NTNT 50 CT	PAT0718100	17	Year(s)	Female Adult	16-Jan-97	REDNESS	US
NOX ORI PAD REG PAD NTNT 50 CT	PUC0718142	11	Year(s)	Female Child	16-Jan-97	BURNING	US
NOX ORI PAD REG PAD NTNT 50 CT	RAS0718290	54	Year(s)	Male Adult	17-Jan-97	STINGING	US
NOX ORI PAD REG PAD NTNT 75 CT	MON0718186		Unknown	Female Adult	17-Jan-97	BOILS	US
NOX ASPTC ASTR REG 8 OZ	HOL0718449		Unknown	Female Adult	21-Jan-97	BLISTERS	US
NOX ASPTC ASTR REG 8 OZ	SIM0718634		Unknown	Female Adult	21-Jan-97	RASH	US
NOX ORI PAD MAX PAD NTNT 50 CT	CAI0718796		Unknown	Female Child	22-Jan-97	RASH	US
NOX ORI PAD MAX PAD NTNT 50 CT	DRO0718868	13	Year(s)	Female Child	22-Jan-97	BURNING	US
NOX ORI PAD MAX PAD NTNT 50 CT	GRA0718842	13	Year(s)	Male Adult	22-Jan-97	PIMPLES	US
NOX ORI PAD MAX PAD NTNT 50 CT	MCK0718818	19	Year(s)	Female Child	22-Jan-97	BURNING	US
D-NOX PADS REG STR ND	ROT0718947	11	Year(s)	Female Child	23-Jan-97	BURNING	US
NOX ORI PAD REG PAD NTNT 50 CT	HID0719013	13	Year(s)	Female Child	23-Jan-97	REDNESS	US
NOXZEMA PADS MAXIMUM STRENGTH ND	RHO0719066	14	Unknown	Male Adult	23-Jan-97	BURNING	US
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0719063		Unknown	Unknown	23-Jan-97	ACNE	US
NOX ORI PAD REG PAD NTNT 50 CT	BRE0719243	30	Year(s)	Unknown	24-Jan-97	ACNE	US

NOX ORI PAD REG PAD NTNT 50 CT	HUD0719235	16	Year(s)	Male Child	24-Jan-97	SORENESS	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	LAM0719387	15	Year(s)	Female Child	27-Jan-97	STINGING	US	N	SKIN	7	Minute(s)
NOX ORI PAD MAX PAD NTNT 50 CT	STE0719316		Unknown	Male Adult	27-Jan-97	SWELLING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	BIC0719748		Unknown	Female Adult	28-Jan-97	ACNE	US	N	SKIN	10	Day(s)
NOX ASPTC ASTR REG 8 OZ	WAL0719963		Unknown	Female Child	29-Jan-97	NONE	US	N	EYE		
NOX ORI PAD REG PAD NTNT 75 CT	MC 0719921		Unknown	Female Child	29-Jan-97	BURNING	US	N	SKIN	1	Minute(s)
D-NOX PADS REG STR ND	WAS0720084	23	Year(s)	Female Adult	30-Jan-97	BURNING	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAR0720069		Unknown	Female Adult	30-Jan-97	RASH	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR REG 8 OZ	JEN0720339	15	Year(s)	Male Child	31-Jan-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	STR0720343	18	Year(s)	Male Adult	31-Jan-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BLA0720323	24	Year(s)	Female Adult	31-Jan-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	JON0720271		Unknown	Female Adult	31-Jan-97	REDNESS	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 50 CT	FRE0720434		Unknown	Female Adult	03-Feb-97	SCRATCH	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BOW0720858		Unknown	Female Child	04-Feb-97	BUMPS	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MC 0720742	15	Year(s)	Male Child	04-Feb-97	BUMPS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MC 0720742		Unknown	Female Adult	04-Feb-97	BUMPS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOR0720857	12	Year(s)	Female Child	04-Feb-97	WELTS	US	N	SKIN		
D-NOX PADS REG STR ND	MC 0721035	11	Year(s)	Male Child	05-Feb-97	HEADACHE	US	N	INHALATION		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	FIT0721042	8	Year(s)	Female Child	05-Feb-97	NONE	US	N	INGESTION		
NOX ORI PAD MAX PAD NTNT 50 CT	POR0720951	15	Year(s)	Male Child	05-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MAC0721178	17	Year(s)	Female Child	06-Feb-97	REDNESS	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 4 OZ	SHE0721196	10	Year(s)	Female Child	07-Feb-97	NONE	US	N	INGESTION		
NOX ORI PAD MAX PAD NTNT 50 CT	COV0721206	17	Year(s)	Male Child	07-Feb-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	JOH0721317		Unknown	Female Child	07-Feb-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOO0721381	17	Year(s)	Female Child	07-Feb-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	PAC0721620	13	Year(s)	Female Child	10-Feb-97	ACNE	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	ROB0721815	13	Year(s)	Female Child	11-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	BUT0721761		Unknown	Male Adult	11-Feb-97	SWELLING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	JOH0721713	15	Year(s)	Female Child	11-Feb-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	KLI0721958		Unknown	Female Adult	12-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	FRE0721994		Unknown	Female Child	12-Feb-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	JAC0721867		Unknown	Female Adult	12-Feb-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	SAN0722152	16	Year(s)	Female Child	13-Feb-97	STINGING	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	HAY0722293		Unknown	Female Adult	14-Feb-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH TOTAL	WOM0722388	16	Year(s)	Male Child	14-Feb-97	ACNE	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	CRA0722408		Unknown	Female Adult	18-Feb-97	BURNING	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	FRE0722464	13	Year(s)	Female Child	18-Feb-97	DRYNESS	US	N	SKIN	2	Week(s)

NOX ASPTC ASTR REG 8 OZ	BAL0722831	17	Year(s)	Female Child	19-Feb-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	MAR0722798		Unknown	Female Adult	19-Feb-97	RASH	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HAG0722826		Unknown	Female Adult	19-Feb-97	ACNE	US	N	SKIN		
D-NOX PADS REG STR ND	TRE0722915	14	Year(s)	Male Child	20-Feb-97	ACNE	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	BAU0723053	15	Year(s)	Male Child	20-Feb-97	PIMPLES	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LOP0722974	18	Year(s)	Male Adult	20-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	PAR0723358	16	Year(s)	Female Adult	24-Feb-97	BUMPS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	KAM0723587	19	Year(s)	Female Adult	25-Feb-97	ACNE	US	N	SKIN	1	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	REE0723502		Unknown	Female Adult	25-Feb-97	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	TRU0723745		Unknown	Unknown	26-Feb-97	STINGING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	RIV0723825	11	Year(s)	Female Child	26-Feb-97	REDNESS	US	N	SKIN	30	Year(s)
NOX ORI PAD REG PAD NTNT 50 CT	MIL0723815		Unknown	Male Adult	26-Feb-97	ACNE	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	SIP0723905	14	Year(s)	Female Child	27-Feb-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	LAM0724291		Unknown	Female Adult	03-Mar-97	ITCHING	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MEE0724315	15	Year(s)	Male Adult	03-Mar-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BUR0724576	12	Year(s)	Female Child	04-Mar-97	ACNE	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	ROB0724611	18	Year(s)	Female Adult	05-Mar-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	BRO0724937	10	Year(s)	Male Child	06-Mar-97	BUMPS	US	N	SKIN	3	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HOL0724956	17	Year(s)	Female Child	06-Mar-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	JET0725062	13	Unknown	Female Child	07-Mar-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	PAC0724992		Unknown	Female Adult	07-Mar-97	RASH	US	N	SKIN	7	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JOH0725394	18	Year(s)	Female Child	10-Mar-97	BUMPS	US	N	SKIN	5	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	PAD0725411	13	Year(s)	Male Child	11-Mar-97	PIMPLES	US	N	SKIN	3	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	JOH0725757	15	Year(s)	Female Child	12-Mar-97	PIMPLES	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	LAR0725922	14	Year(s)	Female Child	13-Mar-97	HIVES	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DAV0726046		Unknown	Female Adult	14-Mar-97	SORES	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	WOJ0726082	12	Year(s)	Female Child	14-Mar-97	RASH	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	WIL0725966		Unknown	Female Adult	14-Mar-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	VAN0726360	15	Year(s)	Female Child	17-Mar-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	CAR0726701		Unknown	Female Adult	19-Mar-97	SORENESS	US	N	SKIN	12	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAR0726763	15	Year(s)	Female Adult	19-Mar-97	PIMPLES	US	N	SKIN	3	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	REF0727004		Unknown	Female Child	20-Mar-97	ACNE	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	TER0727244	34	Year(s)	Female Adult	24-Mar-97	RASH	US	N	SKIN	5	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SMI0727412	11	Year(s)	Female Child	24-Mar-97	REDNESS	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	TOM0727653	12	Year(s)	Female Child	25-Mar-97	RASH	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	VER0727602	13	Year(s)	Male Child	25-Mar-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	VAL0727585		Unknown	Female Child	25-Mar-97	BUMPS	US	N	SKIN	2	Day(s)

NOX ORI PAD MAX PAD NTNT 50 CT	WIL0727703		Unknown	Female Adult	26-Mar-97	TEARING	US	N	EYE INDIRECT		
D-NOX PADS REG STR ND	AGA0727861	43	Year(s)	Female Adult	27-Mar-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	TAS0727947	12	Year(s)	Female Child	27-Mar-97	PIMPLES	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HER0727930		Unknown	Female Child	27-Mar-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	FRI0728030	52	Year(s)	Female Adult	31-Mar-97	RASH	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	FAR0728263	14	Year(s)	Female Child	31-Mar-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	AUE0728297	30	Year(s)	Female Adult	01-Apr-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	GUE0728293	23	Year(s)	Female Adult	01-Apr-97	PIMPLES	US	N	SKIN	6	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	BEC0728642	13	Year(s)	Female Child	02-Apr-97	BUMPS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	NOR0728512	17	Year(s)	Female Adult	02-Apr-97	REDNESS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	WAT0728692	12	Year(s)	Female Adult	03-Apr-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	CHI0729195		Unknown	Male Child	07-Apr-97	PIMPLES	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	TUC0729095		Unknown	Male Adult	07-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HER0729619	12	Year(s)	Female Child	09-Apr-97	ACNE	US	N	SKIN		Unknown
NOX ORI PAD REG PAD NTNT 50 CT	MAR0729563		Unknown	Female Adult	09-Apr-97	REDNESS	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	PEO0729610	13	Year(s)	Female Child	09-Apr-97	RASH	US	N	SKIN	2	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MOO0729625	27	Year(s)	Male Adult	09-Apr-97	SORES	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	MIT0729666		Unknown	Female Adult	10-Apr-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	DOB0729731	14	Unknown	Female Adult	10-Apr-97	DIFFICULTY	US	N	INHALATION		
NOX ORI PAD REG PAD NTNT 50 CT	HAL0729875		Unknown	Female Adult	11-Apr-97	SCRATCH	US	N	INJURY		
NOX ORI PAD MAX PAD NTNT 50 CT	REI0730019		Unknown	Female Adult	14-Apr-97	DISCOLORATION	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	GAR0730421	13	Year(s)	Female Child	15-Apr-97	PEELING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	ARC0730437	28	Year(s)	Female Adult	15-Apr-97	NONE	US	N	ORAL/NASAL		
NOX ASPTC ASTR XTR 8 OZ	STI0730320	16	Year(s)	Female Child	15-Apr-97	REDNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MOR0730358	35	Year(s)	Female Adult	15-Apr-97	IRRITATION	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SAL0730521		Unknown	Female Adult	16-Apr-97	BURN	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	VAN0730782	5	Year(s)	Female Child	17-Apr-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	STE0730660	56	Year(s)	Female Adult	17-Apr-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	HOE0730980		Unknown	Female Adult	18-Apr-97	DRYNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	DON0730842	13	Year(s)	Female Child	18-Apr-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HEC0730937	11	Year(s)	Female Child	18-Apr-97	NAUSEA	US	N	INHALATION		
NOX ORI PAD REG PAD NTNT 50 CT	SCH0731081	18	Year(s)	Male Adult	21-Apr-97	RASH	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	ELL0731492	13	Year(s)	Female Child	22-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ROS0731358		Unknown	Male Adult	22-Apr-97	BURN	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	REF0731572		Unknown	Unknown	23-Apr-97	PIMPLES	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	EHR0731789		Unknown	Female Adult	24-Apr-97	FLAKING	US	N	SKIN	3	Day(s)
D-NOX PADS REG STR ND	RED0732122	11	Year(s)	Male Child	28-Apr-97	IRRITATION	US	N	SKIN	2	Month(s)

NOX ORI PAD MAX PAD NTNT 50 CT	WIL0732230	15	Year(s)	Male Child	28-Apr-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	ROS0732148	16	Year(s)	Male Child	28-Apr-97	ACNE	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	JON0732212	18	Year(s)	Female Adult	28-Apr-97	HAIR LOSS (DIFFUSE)	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	ARA0732382	17	Year(s)	Male Child	29-Apr-97	DRYNESS	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	KOU0732532	16	Year(s)	Female Adult	30-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ROB0732590		Unknown	Female Adult	30-Apr-97	PIMPLES	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	JAC0732520	14	Year(s)	Male Adult	30-Apr-97	BLEMISHES	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	AMO0732683		Unknown	Unknown	01-May-97	DIFFICULTY	US	N	INHALATION	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	LOP0732629	18	Year(s)	Female Child	01-May-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	BAY0733370	13	Year(s)	Female Child	06-May-97	PIMPLES	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LEV0733503	17	Year(s)	Female Child	07-May-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	GON0733598	14	Year(s)	Male Child	12-May-97	DISCOLORATION	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	LOU0733630	15	Year(s)	Female Adult	12-May-97	BURNING	US	N	SKIN		Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	KUM0733942		Unknown	Female Child	12-May-97	STINGING	US	N	SKIN	5	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	MOO0733838	11	Year(s)	Female Child	12-May-97	ACNE	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CRA0733962	22	Year(s)	Female Adult	12-May-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	CAS0733981	16	Year(s)	Male Adult	13-May-97	ACNE	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JUN0734040	13	Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	4	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	LIN0734060		Unknown	Female Adult	13-May-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	HAS0734315	12	Year(s)	Male Child	14-May-97	ACNE	US	N	SKIN	3	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	ROM0734309	30	Year(s)	Female Adult	14-May-97	ACNE	US	N	SKIN	3	Day(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	BRO0734594	3	Year(s)	Female Child	16-May-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR REG 8 OZ	BRA0734606	16	006	Female Child	16-May-97	NONE	US	N	EYE		
NOX ORI PAD MAX PAD NTNT 50 CT	TRA0734522	13	Year(s)	Female Child	16-May-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	DUN0734651		Unknown	Female Adult	19-May-97	SORES	US	Y	SKIN	5	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	SAL0734697		Unknown	Female Child	19-May-97	REDNESS	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	VUC0735038	15	Year(s)	Female Child	20-May-97	RASH	US	N	SKIN	2	Day(s)
D-NOX PADS REG STR ND	FAC0735303		Unknown	Female Adult	21-May-97	CUT, SCRATCH	US	N	INJURY	8	Hour(s)
D-NOX PADS REG STR ND	ROB0735241		Unknown	Female Adult	21-May-97	BURN	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ARM0735268	13	Year(s)	Female Child	21-May-97	RASH	US	N	SKIN	12	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	KEN0735273	19	Unknown	Female Adult	21-May-97	RASH	US	N	SKIN	3	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	PEN0735496	2	Year(s)	Female Child	22-May-97	NONE	US	N	INGESTION		
D-NOX PADS REG STR ND	WIL0735612	17	Year(s)	Female Adult	23-May-97	ACNE	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	CEC0735619		Unknown	Male Adult	23-May-97	ACNE	US	N	SKIN		Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	HER0735618	16	Year(s)	Unknown	23-May-97	PIMPLES	US	N	SKIN	3	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LEV0735544		Unknown	Female Adult	23-May-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	TOY0735601		Unknown	Female Adult	23-May-97	SCRATCH	US	N	INJURY	3	Day(s)

OLAY DAILY RENEWAL LOTION 4 OZ	OSB0784492		Unknown	Female Adult	24-Mar-98	RASH	US	N	SKIN	12	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	SCH0784588		Unknown	Female Adult	24-Mar-98	CRACKING	US	Y	SKIN	10	Unknown
AGE DEFYING SERIES CREAM PACKETTE	LEE0784901		Unknown	Female Adult	25-Mar-98	IRRITATION	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	COA0784804	29	Year(s)	Female Adult	25-Mar-98	SWELLING	CA	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIN0784787	26	Year(s)	Female Adult	25-Mar-98	REDNESS	US	N	SKIN	7	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOL0784928		Unknown	Female Adult	26-Mar-98	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0784998		Unknown	Female Adult	26-Mar-98	BURNING	US	N	EYE		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	LOP0784947	40	Year(s)	Female Adult	26-Mar-98	DRYNESS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0784917		Unknown	Female Adult	26-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0785010		Unknown	Female Adult	26-Mar-98	HEADACHE	US	N	INHALATION	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRO0785151	50	Year(s)	Female Adult	27-Mar-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BLA0785426		Unknown	Female Adult	30-Mar-98	RASH	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0785422		Unknown	Female Adult	30-Mar-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0785383	76	Year(s)	Female Adult	30-Mar-98	ITCHING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSP0785658		Unknown	Male Adult	30-Mar-98	BLISTERS	US	Y	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JER0785674		Unknown	Female Adult	31-Mar-98	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JON0785694		Unknown	Female Adult	31-Mar-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LOS0786076		Unknown	Male Adult	01-Apr-98	BLISTERS	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0786006		Unknown	Female Adult	01-Apr-98	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CON0786233		Unknown	Female Adult	02-Apr-98	REDNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VOC0786253	46	Year(s)	Female Adult	02-Apr-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0786374		Unknown	Female Adult	03-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SWA0786438	52	Year(s)	Female Adult	03-Apr-98	SWELLING	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEL0786843	25	Year(s)	Female Adult	06-Apr-98	REDNESS	US	N	SKIN	24	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ELL0786645	39	Year(s)	Female Adult	06-Apr-98	HIVES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0786679	19	Year(s)	004	06-Apr-98	BUMPS	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	LIS0787033	68	Year(s)	Female Adult	07-Apr-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COS0787103	42	Year(s)	Female Adult	07-Apr-98	SCRATCH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAL0786904	54	Year(s)	Female Adult	07-Apr-98	BUMPS	US	N	SKIN		
AGE DEFYING SERIES CREAM PACKETTE	SAL0787140		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	3	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	YOU0787219		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0787290		Unknown	Female Adult	08-Apr-98	RASH	US	N	SKIN	8	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0787184	56	Year(s)	Female Adult	08-Apr-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DUP0787542		Unknown	Female Adult	09-Apr-98	RASH	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	YER0787589		Unknown	Female Adult	09-Apr-98	HEADACHE	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JON0787888	26	Year(s)	Male Adult	13-Apr-98	DIARRHEA	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	POR0787980		Unknown	Unknown	13-Apr-98	REDNESS	US	Y	SKIN	3	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	BEN0788128		Unknown	Female Adult	14-Apr-98	BUMPS	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOU0788258		Unknown	Female Adult	14-Apr-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NOR0788288	33	Year(s)	Female Adult	14-Apr-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TEM0788188	40	Year(s)	Female Adult	14-Apr-98	HIVES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0788464	40	Year(s)	Female Adult	15-Apr-98	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PET0788362		Unknown	Female Adult	15-Apr-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REF0788564		Unknown	Female Adult	16-Apr-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0788704	36	Year(s)	Female Adult	16-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0788543		Unknown	Female Adult	16-Apr-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLI0788709	30	Year(s)	Female Adult	16-Apr-98	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0788680	45	Unknown	Female Adult	16-Apr-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0788764	47	Year(s)	Female Adult	17-Apr-98	PIMPLES	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ODE0788914		Unknown	Unknown	17-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0789024	37	Year(s)	Female Adult	20-Apr-98	PIMPLES	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SUT0789099	46	Year(s)	Female Adult	20-Apr-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0789336		Unknown	Female Adult	21-Apr-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DI 0789357		Unknown	Female Adult	21-Apr-98	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLA0789604		Unknown	Unknown	22-Apr-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0789739	72	Year(s)	Female Adult	22-Apr-98	WELTS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GUE0790170	26	Year(s)	Female Adult	24-Apr-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0790504	52	Year(s)	Female Adult	27-Apr-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PIE0790524	60	Year(s)	Female Adult	27-Apr-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RUS0790400		Unknown	Female Adult	27-Apr-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SER0790610		Unknown	Male Adult	27-Apr-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FEL0790720	41	Year(s)	Female Adult	28-Apr-98	PIMPLES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRL0790819		Unknown	Female Adult	28-Apr-98	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WEI0790880		Unknown	Unknown	28-Apr-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	YEO0790666		Unknown	Unknown	28-Apr-98	RASH	US	N	SKIN	3	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BRO0790992		Unknown	Unknown	29-Apr-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0790982	67	Year(s)	Female Adult	29-Apr-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DOU0791728	49	Year(s)	Female Adult	04-May-98	SWELLING	US	N	SKIN	10	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HYB0791658		Unknown	Female Adult	04-May-98	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHE0791584		Unknown	Female Adult	04-May-98	BUMPS	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOL0791743		Unknown	Female Adult	04-May-98	STINGING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOE0791606		Unknown	Female Adult	04-May-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OES0791585		Unknown	Female Adult	04-May-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	POO0791882	40	Year(s)	Female Adult	04-May-98	REDNESS	US	N	SKIN	3	Day(s)

AGE DEFYING SERIES CREAM PACKETTE	GRA0792075	39	Year(s)	Female Adult	05-May-98	SWELLING	US	Y	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DUP0792220	48	Year(s)	Female Adult	06-May-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FEN0792225		Unknown	Female Adult	06-May-98	BUMPS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0792361		Unknown	Unknown	06-May-98	BOILS	US	Y	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0792282	38	Year(s)	Female Adult	06-May-98	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	SIT0792396	41	Year(s)	Male Adult	06-May-98	BLISTERS	US	Y	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAR0792503		Unknown	Female Adult	07-May-98	RASH	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	SIE0792453		Unknown	Female Adult	07-May-98	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GRE0792711	26	Year(s)	Female Adult	08-May-98	PIMPLES	CA	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRU0792955		Unknown	Female Adult	11-May-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	SIN0793051		Unknown	Female Adult	11-May-98	PIMPLES	US	Y	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SPI0792830		Unknown	Female Adult	11-May-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COT0793092		Unknown	Female Adult	12-May-98	DRYNESS	US	N	SKIN	2	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0793159	22	Year(s)	Male Adult	12-May-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAG0793135		Unknown	Unknown	12-May-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GLE0793376	27	Year(s)	Female Adult	13-May-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RUS0793396	72	Year(s)	Female Adult	13-May-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHO0793295		Unknown	Female Adult	13-May-98	ACNE	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0793330		Unknown	Unknown	13-May-98	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0793488	33	Year(s)	Female Adult	14-May-98	PEELING	CA	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AWA0793749		Unknown	Female Adult	15-May-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	THO0794188		Unknown	Female Adult	19-May-98	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUC0794588		Unknown	Female Adult	21-May-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAP0794753		Unknown	Unknown	22-May-98	TINGLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VAC0794748	43	Year(s)	Female Adult	22-May-98	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOW0794962		Unknown	Female Adult	26-May-98	PIMPLES	US	N	SKIN	14	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAL0795103		Unknown	Female Adult	26-May-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAD0795113		Unknown	Female Adult	26-May-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ARN0795378	34	Year(s)	Female Adult	27-May-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRO0795223	50	Year(s)	Female Adult	27-May-98	PIMPLES	US	N	SKIN	4	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NOR0795413		Unknown	Male Adult	27-May-98	ALLERGIC REACTION	US	Y	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0795305		Unknown	Female Adult	27-May-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIR0795507	39	Year(s)	Female Adult	28-May-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LUS0795553	15	Year(s)	004	28-May-98	ACNE	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	COB0795810	42	Year(s)	Female Adult	29-May-98	ACNE	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOF0795646	31	Year(s)	Female Adult	29-May-98	SWELLING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0795667		Unknown	Female Adult	29-May-98	REDNESS	US	Y	SKIN	3	Months(s)

OLAY DAILY RENEWAL CREAM 2 OZ	FIT0796031		Unknown	Female Adult	01-Jun-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LIN0796249	42	Year(s)	Female Adult	02-Jun-98	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RAM0796251		Unknown	Female Adult	02-Jun-98	DRYNESS	US	N	SKIN	6	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHA0796265		Unknown	Female Adult	02-Jun-98	SORENESS	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STR0796747		Unknown	Female Adult	04-Jun-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AVE0796776		Unknown	Female Adult	05-Jun-98	REDNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIR0796913		Unknown	Female Adult	05-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NAQ0796841	27	Year(s)	Female Adult	05-Jun-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAL0797145		Unknown	Unknown	08-Jun-98	(GENERALIZED)	US	N	INHALATION		
AGE DEFYING SERIES CREAM PACKETTE	ROO0797407	40	Year(s)	Female Adult	09-Jun-98	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HER0797456		Unknown	Female Adult	09-Jun-98	ACNE	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0797316	24	Year(s)	Female Adult	09-Jun-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0797388		Unknown	Male Adult	09-Jun-98	SUNBURN	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0797629	50	Year(s)	Female Adult	10-Jun-98	HEADACHE	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	HON0797476		Unknown	Female Adult	10-Jun-98	REDNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STR0797542		Unknown	Female Adult	10-Jun-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0797835		Unknown	Female Adult	11-Jun-98	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CZI0797935		Unknown	Female Adult	12-Jun-98	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	COY0798043		Unknown	Female Adult	12-Jun-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0798264		Unknown	Female Adult	15-Jun-98	PEELING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KEN0798412		Unknown	Female Adult	16-Jun-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ESK0798393		Unknown	Female Adult	16-Jun-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0798556		Unknown	Female Adult	16-Jun-98	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KNO0798560		Unknown	Female Adult	16-Jun-98	INFECTION	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	SOL0798742		Unknown	Male Adult	17-Jun-98	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAR0799214		Unknown	Female Adult	19-Jun-98	BUMPS	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LOP0799210		Unknown	Female Adult	19-Jun-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0799092		Unknown	Female Adult	19-Jun-98	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUC0799075		Unknown	Female Adult	19-Jun-98	ACNE	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIZ0799570		Unknown	Female Adult	23-Jun-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FON0799986		Unknown	Female Adult	25-Jun-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0800141		Unknown	Female Adult	25-Jun-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOG0800323		Unknown	Male Adult	26-Jun-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BEL0800761		Unknown	Female Adult	30-Jun-98	BLISTERS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LA 0800801	26	Year(s)	Female Adult	30-Jun-98	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JEP0801648		Unknown	Female Adult	06-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOS0801672	47	Year(s)	Male Adult	06-Jul-98	BLISTERS	US	Y	SKIN	5	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	MOR0801639		Unknown	Unknown	06-Jul-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ALB0801906		Unknown	Female Adult	07-Jul-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	DUC0801813	35	Year(s)	Female Adult	07-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0801743	57	Year(s)	Female Adult	07-Jul-98	STINGING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0803080		Unknown	Female Adult	13-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOS0803347	48	Year(s)	Female Adult	14-Jul-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSK0803346		Unknown	Female Adult	14-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SIR0803507	47	Year(s)	Female Adult	15-Jul-98	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DI 0803710	45	Year(s)	Female Adult	16-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIT0803730		Unknown	Female Adult	16-Jul-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUM0803832	36	Year(s)	Female Adult	16-Jul-98	CRACKING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REV0803990		Unknown	Female Adult	17-Jul-98	SWELLING	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUC0804389		Unknown	Female Adult	20-Jul-98	STINGING	US	N	EYE		
OLAY DAILY RENEWAL CREAM 2 OZ	LYS0804358	73	Year(s)	Female Adult	20-Jul-98	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ARA0804938		Unknown	Female Adult	22-Jul-98	PEELING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STO0804930		Unknown	Female Adult	22-Jul-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEN0805313		Unknown	Female Adult	23-Jul-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0805096		Unknown	Female Adult	23-Jul-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NET0805985		Unknown	Female Adult	28-Jul-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SON0806436		Unknown	Female Adult	29-Jul-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ALT0806606		Unknown	Female Adult	30-Jul-98	ALLERGIC REACTION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RAN0807650		Unknown	Female Adult	05-Aug-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUT0808111		Unknown	Female Adult	07-Aug-98	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0808754		Unknown	Female Adult	11-Aug-98	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VAL0808796		Unknown	Female Adult	11-Aug-98	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	JEC0808929		Unknown	Female Adult	12-Aug-98	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0808995	62	Year(s)	Female Adult	12-Aug-98	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0809214		Unknown	Unknown	13-Aug-98	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOE0809346		Unknown	Female Adult	13-Aug-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0809667	46	Year(s)	Female Adult	17-Aug-98	CRACKING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SKA0809851		Unknown	Female Adult	17-Aug-98	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUR0809991		Unknown	Female Adult	18-Aug-98	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAN0810020	23	Year(s)	Female Adult	18-Aug-98	HIVES	US	Y	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	UNK0810587	45	Year(s)	Female Adult	20-Aug-98	SWELLING	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAB0811330		Unknown	Female Adult	25-Aug-98	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FOR0811566	67	Year(s)	Female Adult	26-Aug-98	WELTS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOD0811478		Unknown	Female Adult	26-Aug-98	SNEEZING	US	N	INHALATION		

OLAY DAILY RENEWAL CREAM 2 OZ	LAR0811718		Unknown	Female Adult	27-Aug-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0812052	35	Year(s)	Female Adult	28-Aug-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OUL0811940	54	Year(s)	Female Adult	28-Aug-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEC0812591		Unknown	Male Adult	01-Sep-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOD0812681		Unknown	Female Adult	02-Sep-98	REDNESS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0812740		Unknown	Female Adult	02-Sep-98	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REH0812654	42	Year(s)	Female Adult	02-Sep-98	RASH	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ELL0813232		Unknown	Female Adult	04-Sep-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0813607	44	Year(s)	Female Adult	08-Sep-98	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CRO0813325	53	Year(s)	Female Adult	08-Sep-98	SWELLING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRE0813404		Unknown	Female Adult	08-Sep-98	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0813724	80	Year(s)	Female Adult	09-Sep-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0813827		Unknown	Female Adult	10-Sep-98	ACNE	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALL0814037		Unknown	Female Adult	11-Sep-98	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	YER0814327	57	Year(s)	Female Adult	14-Sep-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOR0814344	43	Year(s)	Female Adult	14-Sep-98	DRYNESS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DIC0814274		Unknown	Female Adult	14-Sep-98	SCRATCH	US	N	INJURY	14	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EWA0814396	41	Year(s)	Female Adult	14-Sep-98	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VAN0814287		Unknown	Female Adult	14-Sep-98	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PHI0814857	44	Year(s)	Female Adult	16-Sep-98	BLISTERS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FOS0814995		Unknown	Female Adult	17-Sep-98	SWELLING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SHA0815048		Unknown	Female Adult	17-Sep-98	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0815378		Unknown	Female Adult	21-Sep-98	REDNESS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHE0815578		Unknown	Female Adult	22-Sep-98	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	.0815836		Unknown	Female Adult	23-Sep-98	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRA0815890		Unknown	Female Adult	23-Sep-98	PIMPLES	US	N	SKIN	30	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIE0815914	65	Year(s)	Female Adult	24-Sep-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	VUK0816071		Unknown	Female Adult	24-Sep-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0816254	48	Year(s)	Female Adult	25-Sep-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0816166	35	Year(s)	Female Adult	25-Sep-98	ACNE	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAE0816581	40	Year(s)	Female Adult	29-Sep-98	RASH	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEM0816908	75	Year(s)	Female Adult	30-Sep-98	DISCOLORATION	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUN0817148		Unknown	Unknown	02-Oct-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WES0817485	34	Year(s)	Female Adult	05-Oct-98	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRE0817962	82	Year(s)	Female Adult	07-Oct-98	SWELLING	US	Y	SKIN	10	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROS0817858		Unknown	Female Adult	07-Oct-98	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUC0817926		Unknown	Female Adult	07-Oct-98	ACNE	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	CLA0818118		Unknown	Female Adult	08-Oct-98	HIVES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HEI0818330		Unknown	Female Adult	09-Oct-98	ITCHING	US	N	INHALATION	30	002
OLAY DAILY RENEWAL CREAM 2 OZ	KAN0818399		Unknown	Female Adult	09-Oct-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0818345	28	Year(s)	Female Adult	09-Oct-98	DISCOLORATION	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOO0818568	53	Year(s)	Female Adult	12-Oct-98	WRINKLES	US	N	SKIN	1.5	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TEM0819009		Unknown	Female Adult	14-Oct-98	SWELLING	US	N	SKIN	6	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CHA0819198		Unknown	Unknown	15-Oct-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0819555	45	Year(s)	Female Adult	19-Oct-98	SWELLING	US	N	SKIN	3.3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0819922		Unknown	Female Adult	20-Oct-98	SWELLING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	PRA0819960		Unknown	Female Adult	20-Oct-98	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEG0819874		Unknown	Female Adult	20-Oct-98	CONGESTION	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0820612		Unknown	Female Adult	23-Oct-98	DRYNESS	US	N	SKIN		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GAN0820546	63	Year(s)	Female Adult	23-Oct-98	BLEMISHES	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	LOU0820769		Unknown	Female Adult	26-Oct-98	DRYNESS	CA	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	WOR0821074		Unknown	Female Adult	27-Oct-98	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0821284	34	Year(s)	Female Adult	28-Oct-98	BUMPS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CRU0822438		Unknown	Female Adult	04-Nov-98	FLAKING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0823283	38	Year(s)	Female Adult	09-Nov-98	BUMPS	CA	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	MAS0823478		Unknown	Female Adult	10-Nov-98	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUR0823399		Unknown	Female Adult	10-Nov-98	DRYNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FUR0823419		Unknown	Unknown	10-Nov-98	PIMPLES	US	N	SKIN	3.5	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAW0823467	72	Year(s)	Female Adult	10-Nov-98	TEARING	CA	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0823709	89	Year(s)	Female Adult	11-Nov-98	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0823617		Unknown	Female Adult	11-Nov-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DOY0823650		Unknown	Female Adult	11-Nov-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	EVE0823633		Unknown	Female Adult	11-Nov-98	RASH	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0823843	21	Year(s)	Female Adult	12-Nov-98	PIMPLES	CA	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0823868	66	Year(s)	Female Adult	12-Nov-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MON0823860	27	Year(s)	Female Adult	12-Nov-98	SWELLING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DOM0824084	62	Year(s)	Female Adult	13-Nov-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	GEL0824137		Unknown	Unknown	13-Nov-98	DRYNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0824211		Unknown	Female Adult	13-Nov-98	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0824422		Unknown	Female Adult	16-Nov-98	BURNING	US	Y	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOD0825093		Unknown	Female Adult	18-Nov-98	DERMATITIS	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HUM0824894	42	Year(s)	Female Adult	18-Nov-98	PIMPLES	US	N	SKIN	1	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	SCH0825496		Unknown	Female Adult	20-Nov-98	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	HOU0825809		Unknown	Female Adult	23-Nov-98	SORES	US	N	SKIN	2	Months(s)

OLAY DAILY RENEWAL CREAM 2 OZ	MAR0825563	38	Year(s)	Female Adult	23-Nov-98	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	O^N0825784	25	Year(s)	Female Adult	23-Nov-98	FLAKING	US	N	SKIN	5	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RUE0826459	40	Year(s)	Female Adult	30-Nov-98	SWELLING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAR0826811	82	Year(s)	Female Adult	01-Dec-98	SWEAT	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	SAM0826784		Unknown	Unknown	01-Dec-98	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SNO0826759		Unknown	Female Adult	01-Dec-98	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0826771		Unknown	Female Adult	01-Dec-98	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	EOP0827007	50	Year(s)	Female Adult	02-Dec-98	SWELLING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAM0826995		Unknown	Female Adult	02-Dec-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0827160	75	Year(s)	Female Adult	03-Dec-98	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0827168	35	Year(s)	Female Adult	03-Dec-98	SWELLING	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0827358		Unknown	Female Adult	04-Dec-98	FLUSHED	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0827500		Unknown	Unknown	04-Dec-98	BUMPS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PRE0827504		Unknown	Female Adult	04-Dec-98	REDNESS	CA	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ESA0827735	33	Year(s)	Female Adult	07-Dec-98	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COT0828028	22	Year(s)	Female Adult	08-Dec-98	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIR0827885	26	Year(s)	Female Adult	08-Dec-98	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAM0828235		Unknown	Male Adult	09-Dec-98	WRINKLES	US	N	SKIN	9	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AZI0828406		Unknown	Female Adult	10-Dec-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAW0828285	74	Year(s)	Female Adult	10-Dec-98	FLAKING	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCH0828936		Unknown	Female Adult	14-Dec-98	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0828741	34	Year(s)	Female Adult	14-Dec-98	BUMPS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PER0829110	24	Year(s)	Female Adult	15-Dec-98	PIMPLES	CA	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0829010		Unknown	Female Adult	15-Dec-98	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NIC0829193	46	Year(s)	Female Adult	16-Dec-98	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GID0829376		Unknown	Female Adult	17-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MC 0829875	57	Year(s)	Female Adult	21-Dec-98	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0829794		Unknown	Female Adult	21-Dec-98	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WHI0829933		Unknown	Female Adult	21-Dec-98	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ANK0830303		Unknown	Unknown	28-Dec-98	IRRITATION	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0830621		Unknown	Female Adult	28-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0830544	39	Year(s)	Male Adult	28-Dec-98	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAY0830544	39	Year(s)	Male Adult	28-Dec-98	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEN0831353		Unknown	Female Adult	04-Jan-99	STINGING	US	N	INHALATION	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	MCL0831283	37	Year(s)	Female Adult	04-Jan-99	DRYNESS	CA	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VIS0831523		Unknown	Female Adult	05-Jan-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PIT0831886		Unknown	Female Adult	06-Jan-99	DRYNESS	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	PRI0832017		Unknown	Female Adult	06-Jan-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ECK0832092		Unknown	Unknown	07-Jan-99	SNEEZING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	FOS0832158		Unknown	Male Adult	07-Jan-99	SWELLING	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HER0832162	44	Year(s)	Female Adult	07-Jan-99	PIMPLES	US	N	SKIN	11	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0832249	40	Year(s)	Female Adult	07-Jan-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CUR0832392		Unknown	Female Adult	08-Jan-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0832305	29	Year(s)	Female Adult	08-Jan-99	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEA0832723		Unknown	Female Adult	11-Jan-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RAY0832548	30	Year(s)	Female Adult	11-Jan-99	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAE0832749		Unknown	Female Adult	11-Jan-99	PEELING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	REI0832607		Unknown	Female Adult	11-Jan-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AIK0833066	35	Year(s)	Female Adult	12-Jan-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAS0833239	70	Year(s)	Female Adult	13-Jan-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0833636	39	Year(s)	Female Adult	15-Jan-99	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	FAU0833820	70	Year(s)	Female Adult	19-Jan-99	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIU0833724		Unknown	Female Adult	19-Jan-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0834133		Unknown	Female Adult	20-Jan-99	HIVES	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0834312		Unknown	Female Adult	20-Jan-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRU0834260	71	Year(s)	Female Adult	20-Jan-99	BLEMISHES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BEL0834463	25	Year(s)	Female Adult	21-Jan-99	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0834497		Unknown	Female Adult	21-Jan-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0834560		Unknown	Female Adult	21-Jan-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FRA0834616		Unknown	Female Adult	22-Jan-99	BLISTERS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOS0834715		Unknown	Female Adult	22-Jan-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAY0834883		Unknown	Female Adult	25-Jan-99	DRYNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAL0834930		Unknown	Female Adult	25-Jan-99	RASH	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KUN0835417	45	Year(s)	Female Adult	27-Jan-99	HEADACHE	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FIL0835790		Unknown	Female Adult	28-Jan-99	BURN	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SAU0835664	42	Year(s)	Female Adult	28-Jan-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEM0835831		Unknown	Female Adult	28-Jan-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAM0835819	52	Year(s)	Female Adult	28-Jan-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0835722	70	Year(s)	Female Adult	28-Jan-99	REDNESS	CA	N	EYE	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAL0835960	64	Year(s)	Female Adult	29-Jan-99	REDNESS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOE0835856		Unknown	Female Adult	29-Jan-99	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ACK0836091	78	Year(s)	Female Adult	01-Feb-99	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	EDI0836304		Unknown	Male Adult	01-Feb-99	RASH	US	N	SKIN	15	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0836241	70	Year(s)	Female Adult	01-Feb-99	DRYNESS	US	N	SKIN	2	Day(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEO0836380	44	Year(s)	Female Adult	02-Feb-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COU0836401		Unknown	Female Adult	02-Feb-99	DISCOLORATION	US	N	SKIN	4	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0836388	51	Year(s)	Female Adult	02-Feb-99	OTHER	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAC0836714	44	Year(s)	Female Adult	03-Feb-99	RASH	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KUN0837062		Unknown	Female Adult	04-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEM0836942		Unknown	Unknown	04-Feb-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEX0836929		Unknown	Female Adult	04-Feb-99	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SMI0837249		Unknown	Female Adult	05-Feb-99	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0837287	41	Year(s)	Female Adult	05-Feb-99	REDNESS	CA	N	SKIN		Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OLS0837289	68	Year(s)	Female Adult	05-Feb-99	REDNESS	US	N	EYE	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIL0837288		Unknown	Female Adult	05-Feb-99	RASH	US	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GIR0837373	29	Year(s)	Female Adult	08-Feb-99	REDNESS	CA	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRU0837948		Unknown	Female Adult	10-Feb-99	DRYNESS	US	N	EYE	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COM0837957	69	Year(s)	Female Adult	10-Feb-99	HIVES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FLA0837945		Unknown	Female Adult	10-Feb-99	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TID0838131		Unknown	Female Adult	10-Feb-99	BUMPS	US	N	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	URS0838249		Unknown	Female Adult	11-Feb-99	BURNING	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAT0838210	67	Year(s)	Female Adult	11-Feb-99	DIFFICULTY	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	LAR0838327		Unknown	Female Adult	11-Feb-99	REDNESS	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GRA0838626		Unknown	Female Adult	16-Feb-99	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	VIN0838710		Unknown	Female Adult	16-Feb-99	CRACKING	US	N	SKIN	6	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEI0838942	43	Year(s)	Female Adult	17-Feb-99	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ADI0839116	40	Year(s)	Female Adult	17-Feb-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0839298	33	Year(s)	Female Adult	18-Feb-99	SWELLING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PER0839149	52	Year(s)	Female Adult	18-Feb-99	BUMPS	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WOL0839374	22	Year(s)	Female Adult	18-Feb-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PAR0839908	50	Year(s)	Female Adult	22-Feb-99	BURNING	CA	N	SKIN	14	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0839930		Unknown	Female Adult	22-Feb-99	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEA0840065		Unknown	Female Adult	23-Feb-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	YAN0840329		Unknown	Female Adult	24-Feb-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0840523	42	Year(s)	Female Adult	25-Feb-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAK0840684	78	Year(s)	Female Adult	25-Feb-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HEA0840933		Unknown	Female Adult	26-Feb-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BAL0841238	36	Year(s)	Female Adult	01-Mar-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BHA0841146		Unknown	Male Adult	01-Mar-99	DISCOLORATION	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0841047		Unknown	Female Adult	01-Mar-99	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	STA0841250	70	Year(s)	Female Adult	01-Mar-99	PIMPLES	US	Y	SKIN	2	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DOM0841410		Unknown	Unknown	02-Mar-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAL0841438	55	Year(s)	Female Adult	02-Mar-99	DIZZINESS	CA	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLO0841753		Unknown	Female Adult	03-Mar-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NUT0842102		Unknown	Female Adult	05-Mar-99	SWELLING	US	N	SKIN		Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOI0842392	49	Year(s)	Female Adult	08-Mar-99	BURNING	US	N	SKIN	9	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PET0842547	50	Year(s)	Female Adult	08-Mar-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SNE0842552		Unknown	Male Adult	08-Mar-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRI0842473	31	Year(s)	Female Adult	08-Mar-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SWE0842482	44	Year(s)	Female Adult	08-Mar-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAY0842821		Unknown	Female Adult	09-Mar-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEN0842860		Unknown	Female Adult	09-Mar-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0842921	51	Year(s)	Female Adult	09-Mar-99	DRYNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUF0843123		Unknown	Unknown	10-Mar-99	PEELING	CA	N	SKIN		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUM0843051	64	Year(s)	Female Adult	10-Mar-99	SWELLING	CA	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COL0843462		Unknown	Unknown	11-Mar-99	REDNESS	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAF0843452		Unknown	Unknown	11-Mar-99	BURNING	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOS0843567		Unknown	Female Adult	12-Mar-99	FLAKING	US	N	SKIN	2	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DED0843610		Unknown	Female Adult	12-Mar-99	BUMPS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0843667		Unknown	Female Adult	12-Mar-99	DRYNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0843735		Unknown	Female Adult	12-Mar-99	RASH	US	N	SKIN	5	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	SAN0843988		Unknown	004	15-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GIL0844002		Unknown	Female Adult	15-Mar-99	BUMPS	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAL0843840	68	Year(s)	Female Adult	15-Mar-99	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	OLI0843945		Unknown	Female Adult	15-Mar-99	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0844221		Unknown	Female Adult	16-Mar-99	BURNING	US	N	EYE INDIRECT	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0844501	71	Year(s)	Female Adult	17-Mar-99	WRINKLES	US	N	SKIN		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAL0844711		Unknown	Female Adult	18-Mar-99	SWELLING	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUN0844716		Unknown	Unknown	18-Mar-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HUN0845002		Unknown	Female Adult	19-Mar-99	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ADA0845623	40	Year(s)	Female Adult	23-Mar-99	ACNE	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TOR0845733		Unknown	Female Adult	23-Mar-99	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIT0845774	76	Year(s)	Unknown	23-Mar-99	REDNESS	US	Y	EYE INDIRECT	8	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIO0845575	51	Year(s)	Female Adult	23-Mar-99	DRYNESS	CA	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLA0846020	22	Year(s)	Female Adult	24-Mar-99	RASH	CA	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0846228		Unknown	Unknown	25-Mar-99	INFLAMED	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAH0846355	50	Year(s)	Female Adult	26-Mar-99	BUMPS	CA	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TAT0846995	59	Year(s)	Female Adult	30-Mar-99	CHAPPED	US	N	SKIN		

AGE DEFYING SERIES CREAM PACKETTE	REF0847434		Unknown	004	31-Mar-99	RASH	US	N	SKIN	12	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEI0847388		Unknown	Female Adult	31-Mar-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0847609		Unknown	Female Adult	01-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAT0847731	43	Year(s)	Female Adult	05-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	YOU0848463	45	Year(s)	Male Adult	07-Apr-99	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0848515		Unknown	Unknown	08-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FRE0848672	44	Year(s)	Female Adult	08-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEB0848563	32	Year(s)	Female Adult	08-Apr-99	BUMPS	CA	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NEL0848827			Female Adult	09-Apr-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STE0849006		Unknown	Female Adult	12-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HER0848974		Unknown	Female Adult	12-Apr-99	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CIC0849479		Unknown	Female Adult	13-Apr-99	BUMPS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOO0849462		Unknown	Female Adult	13-Apr-99	PEELING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0849296	64	Year(s)	Female Adult	13-Apr-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ULL0849706		Unknown	Male Adult	14-Apr-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0849899		Unknown	Female Adult	15-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0849834		Unknown	Unknown	15-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ILV0849960	40	Year(s)	Male Adult	15-Apr-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LEE0849802		Unknown	Female Adult	15-Apr-99	BLEMISHES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0850400	70	Year(s)	Female Adult	19-Apr-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAD0850591		Unknown	Female Adult	19-Apr-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LAC0850335		Unknown	Female Adult	19-Apr-99	FLAKING	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0850373	66	Year(s)	Female Adult	19-Apr-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ECH0850802		Unknown	Female Adult	20-Apr-99	REDNESS	US	N	SKIN	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	PRI0850632		Unknown	Female Adult	20-Apr-99	RASH	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRU0850889		Unknown	Female Adult	21-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	TOW0853962			Female Adult	21-Apr-99	BURNING	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCH0851733		Unknown	Female Adult	26-Apr-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BLE0851550		Unknown	Female Adult	26-Apr-99	SWELLING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	AME0851893		Unknown	Female Adult	27-Apr-99	BUMPS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEN0851953	31	Year(s)	Female Adult	27-Apr-99	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0852048		Unknown	Female Adult	27-Apr-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FAL0852139		Unknown	Female Adult	28-Apr-99	BURNING	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAL0852359	51	Year(s)	Female Adult	29-Apr-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0852526		Unknown	Female Adult	29-Apr-99	REDNESS	US	N	EYE		Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0852923	50	Year(s)	Female Adult	03-May-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROG0852933		Unknown	Female Adult	03-May-99	PIMPLES	US	N	SKIN	1	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VAI0853218	65	Year(s)	Female Adult	04-May-99	BURNING	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PER0853144		Unknown	Female Adult	04-May-99	RASH	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0853417		Unknown	Female Adult	05-May-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MOY0853863		Unknown	Female Adult	07-May-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COL0853755	59	Year(s)	Female Adult	07-May-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LA 0854266		Unknown	Female Adult	10-May-99	REDNESS	US	N	SKIN	15	002
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ESC0854421		Unknown	Female Adult	11-May-99	BOILS	US	N	SKIN	6	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAR0854583		Unknown	Female Adult	12-May-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BUI0854650		Unknown	Female Adult	12-May-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0854662		Unknown	Female Adult	12-May-99	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GER0854915	39	Year(s)	Female Adult	13-May-99	REDNESS	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SIE0854984		Unknown	Unknown	14-May-99	REDNESS	US	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROB0856171		Unknown	Unknown	20-May-99	FLAKING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAN0856637	41	Year(s)	Female Adult	24-May-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	NEI0857662		Unknown	Female Adult	28-May-99	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KOH0857978		Unknown	Male Adult	01-Jun-99	DERMATITIS	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAL0858334	80	Year(s)	Female Adult	03-Jun-99	PEELING	US	N	SKIN	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TYL0858396		000	Unknown	03-Jun-99	BURNING	US	Y	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DEM0858624	65	Year(s)	Female Adult	04-Jun-99	TINGLING	US	N	SKIN	4	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEY0858688		Unknown	Female Adult	04-Jun-99	PIMPLES	US	Y	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JIN0858587		Unknown	Female Adult	04-Jun-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ANT0859007			Female Adult	07-Jun-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DUC0859081	49	Year(s)	Female Adult	07-Jun-99	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUL0859255	40	Year(s)	Female Adult	08-Jun-99	BLISTERS	US	Y	SKIN	8	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAT0859532		Unknown	Female Adult	10-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	POR0860202		Unknown	Female Adult	14-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	THO0860054		Unknown	Female Adult	14-Jun-99	REDNESS	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0859985		Unknown	Female Adult	14-Jun-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0860797		Unknown	Female Adult	17-Jun-99	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0861641	62	Year(s)	Female Adult	23-Jun-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SES0861857		Unknown	Unknown	24-Jun-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAY0861968	35	Year(s)	Female Adult	24-Jun-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KEL0862119		Unknown	Female Adult	25-Jun-99	PIMPLES	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STA0862207		Unknown	Female Adult	25-Jun-99	TIGHTNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAN0862782		Unknown	Female Adult	29-Jun-99	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	QUE0862715		Unknown	Female Adult	29-Jun-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SUN0862747		Unknown	Male Adult	29-Jun-99	RASH	US	Y	SKIN	1	Week(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GAR0862983	69	Year(s)	Female Adult	30-Jun-99	REDNESS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEN0862984		Unknown	Female Adult	30-Jun-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0863075		Unknown	Female Adult	01-Jul-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUG0863523		Unknown	Female Adult	06-Jul-99	BURNING	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REF0863784		Unknown	Female Adult	07-Jul-99	PEELING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SHA0863745		Unknown	Female Adult	07-Jul-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CRC0863731	58	Year(s)	Female Adult	07-Jul-99	CUT	CA	N	INJURY		
OLAY DAILY RENEWAL CREAM 2 OZ	TOR0864233		Unknown	Female Adult	09-Jul-99	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AND0864546		Unknown	Female Adult	12-Jul-99	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FUL0865062		Unknown	Female Adult	15-Jul-99	BURNING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REI0865678			Female Adult	19-Jul-99	CYST	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FIS0865850		Unknown	Male Adult	20-Jul-99	RASH	US	N	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAL0865842	57	Year(s)	Female Adult	20-Jul-99	PIMPLES	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POT0866394	60	Year(s)	Female Adult	23-Jul-99	TEARING	CA	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	AHN0866960	32	Year(s)	004	27-Jul-99	ITCHING	CA	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KLE0867801		Unknown	Female Adult	02-Aug-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	OSB0867673	72	Year(s)	Female Adult	02-Aug-99	BURNING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0868000		Unknown	Female Adult	03-Aug-99	BURNING	US	N	EYE INDIRECT	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAU0868536		Unknown	Female Adult	06-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OSE0868467	34	Year(s)	Female Adult	06-Aug-99	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TUC0868611		Unknown	Female Adult	06-Aug-99	BURNING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOL0868795		Unknown	Female Adult	09-Aug-99	PIMPLES	US	N	SKIN	1	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VER0869126		Unknown	Female Adult	10-Aug-99	BUMPS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THA0870027		Unknown	Female Adult	17-Aug-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0870285		Unknown	Female Adult	19-Aug-99	STINGING/BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BEA0870497		Unknown	Unknown	20-Aug-99	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCO0870550		Unknown	Female Adult	20-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WER0870459		Unknown	Female Adult	20-Aug-99	IRRITATION	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NGU0870800	30	Year(s)	Female Adult	23-Aug-99	SWELLING	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PAS0871244		Unknown	Female Adult	25-Aug-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STE0871556		Unknown	Female Adult	27-Aug-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAU0872089		Unknown	Female Adult	31-Aug-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	VER0872143		Unknown	Female Adult	31-Aug-99	RASH	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NAZ0872526	53	Year(s)	Female Adult	02-Sep-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0872519		Unknown	Female Adult	02-Sep-99	ITCHING	US	N	SKIN	3	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KOT0872525		Unknown	Female Adult	02-Sep-99	BURNING	US	N	SKIN	3	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0872775		Unknown	Female Adult	03-Sep-99	STINGING	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	WAG0872679		Unknown	Female Adult	03-Sep-99	ITCHING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIV0872988		Unknown	Female Adult	07-Sep-99	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TIN0873345	40	Year(s)	Female Adult	09-Sep-99	RASH	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL LOTION 4 OZ	GER0874057		Unknown	Female Adult	14-Sep-99	DIFFICULTY	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUR0874377	75	Year(s)	Female Adult	15-Sep-99	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KNA0874326		Unknown	Unknown	15-Sep-99	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUN0874557		Unknown	Female Adult	16-Sep-99	RASH	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CLE0874910		Unknown	Female Adult	20-Sep-99	BURNING	US	N	SKIN	6	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DER0874976	64	Year(s)	Female Adult	20-Sep-99	SORENESS	CA	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STE0874802		Unknown	Female Adult	20-Sep-99	HEADACHE	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOR0875343		Unknown	Female Adult	22-Sep-99	NONE	US	N	INGESTION		
OLAY DAILY RENEWAL CREAM 2 OZ	CAS0875443		Unknown	Female Adult	22-Sep-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ELM0875307	73	Year(s)	Female Adult	22-Sep-99	BURNING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TER0875405	71	Year(s)	Female Adult	22-Sep-99	BURNING	US	N	SKIN		Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROT0875930		Unknown	Female Adult	27-Sep-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0876617		Unknown	Female Adult	30-Sep-99	BUMPS	US	N	SKIN	2	Week(s)
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	HOS0876778		Unknown	Female Adult	01-Oct-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ALM0876756	36	Year(s)	Female Adult	01-Oct-99	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LAU0877033		Unknown	Female Adult	04-Oct-99	PEELING	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JOS0877398		Unknown	Male Adult	05-Oct-99	RASH	US	Y	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0877476		Unknown	Female Adult	06-Oct-99	SWELLING	US	N	SKIN	1	007
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0877476		Unknown	Female Adult	06-Oct-99	SWELLING	US	N	SKIN	1	007
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0877689		Unknown	Female Adult	07-Oct-99	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEV0877970		Unknown	Female Adult	08-Oct-99	REDNESS	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COZ0878396		Unknown	Female Adult	12-Oct-99	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DE 0878455		Unknown	Female Adult	12-Oct-99	DRYNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FER0878654		Unknown	Female Adult	13-Oct-99	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0878890	64	Year(s)	Female Adult	14-Oct-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOD0879203			Female Adult	18-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CRU0879572		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	STO0879493		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAT0879525		Unknown	Female Adult	19-Oct-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRU0879965		Unknown	Female Adult	21-Oct-99	BURNING	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOO0880087	33	Year(s)	Female Adult	22-Oct-99	BURNING	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0880130		Unknown	Female Adult	22-Oct-99	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOO0880645		Unknown	Female Adult	26-Oct-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAR0880881	83	Year(s)	Female Adult	28-Oct-99	BURNING	US	N	SKIN		

OLAY DAILY RENEWAL CREAM 2 OZ	BIS0881294		Unknown	Female Adult	01-Nov-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEA0882321		Unknown	Female Adult	08-Nov-99	STINGING/BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAN0882687		Unknown	Female Adult	09-Nov-99	REDNESS	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0883011		Unknown	Female Adult	11-Nov-99	BUMPS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COL0883963		Unknown	Female Adult	17-Nov-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LOG0884236		Unknown	Female Adult	18-Nov-99	BUMPS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAS0884345		Unknown	Female Adult	19-Nov-99	DRYNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAG0884302	44	Year(s)	Female Adult	19-Nov-99	PIMPLES	US	Y	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DEP0884738		Unknown	Female Adult	23-Nov-99	REDNESS	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PHI0884919		Unknown	Female Adult	24-Nov-99	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0885591		Unknown	Female Adult	30-Nov-99	BURNING	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CUR0885731		Unknown	Female Adult	01-Dec-99	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RYA0885688		Unknown	Female Adult	01-Dec-99	ACNE	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ATW0885817		Unknown	Female Adult	01-Dec-99	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SCA0886016		Unknown	Female Adult	02-Dec-99	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GAR0886002		Unknown	Male Adult	02-Dec-99	BLISTERS	US	Y	SKIN	10	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0886586		Unknown	Female Adult	07-Dec-99	BLISTERS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOD0886473	62	Year(s)	Female Adult	07-Dec-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PLA0886933	39	Year(s)	Female Adult	09-Dec-99	PEELING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	COV0887131	45	Year(s)	Male Adult	10-Dec-99	BLISTERS	US	Y	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SOK0887077		Unknown	Female Adult	10-Dec-99	ITCHING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GRO0887209		Unknown	Female Adult	13-Dec-99	COUGHING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	BAC0887500		Unknown	Female Adult	14-Dec-99	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DOL0887591		Unknown	Female Adult	15-Dec-99	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	LON0887717		Unknown	Female Adult	15-Dec-99	REDNESS	US	N	SKIN	2	Months(s)
OLAY DAILY RENEWAL LOTION 4 OZ	EMM0888047	36	Year(s)	Female Adult	20-Dec-99	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0888304		Unknown	Female Adult	21-Dec-99	BURNING	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	COR0888576	66	Year(s)	Female Adult	22-Dec-99	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SIM0888612		Unknown	Female Adult	22-Dec-99	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EVA0889072	68	Year(s)	Female Adult	29-Dec-99	BURNING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DIA0889286		Unknown	Female Adult	30-Dec-99	ITCHING	US	Y	SKIN	10	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REY0889388		Unknown	Female Adult	30-Dec-99	BURNING	US	N	SKIN	10	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FLE0889597		Unknown	Female Adult	04-Jan-00	BUMPS	US	N	SKIN		Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WEB0889955		Unknown	Female Adult	06-Jan-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	AND0889927		Unknown	Female Adult	06-Jan-00	BURNING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PRE0890074	44	Year(s)	Female Adult	06-Jan-00	SWELLING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FAR0890163		Unknown	Female Adult	07-Jan-00	BURNING	US	N	SKIN	1	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	PIK0890174		Unknown	Female Adult	07-Jan-00	RASH	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	STU0890190		Unknown	Female Adult	07-Jan-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	QUI0890595	31	Year(s)	Female Adult	10-Jan-00	UNKNOWN	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AVI0890463	37	Year(s)	Male Adult	10-Jan-00	RASH	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEL0890379		Unknown	Female Adult	10-Jan-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MIL0890739	37	Year(s)	Female Adult	11-Jan-00	SWELLING	CA	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	AND0890888		Unknown	Female Adult	12-Jan-00	FLAKING	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	RIC0890969		000	Male Adult	12-Jan-00	RASH	US	Y	SKIN	1	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	BRO0891129			Female Adult	13-Jan-00	BURNING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0891090		Unknown	Female Adult	13-Jan-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAZ0891831	45	Year(s)	Female Adult	19-Jan-00	PIMPLES	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0891668		Unknown	Female Adult	19-Jan-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0891983	56	Year(s)	Female Adult	20-Jan-00	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROB0892108		Unknown	Female Adult	21-Jan-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0892468		Unknown	Female Adult	24-Jan-00	PIMPLES	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0892312		Unknown	Female Adult	24-Jan-00	FLAKING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOL0892465		Unknown	Female Adult	24-Jan-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BEI0892496		Unknown	Female Adult	25-Jan-00	REDNESS	US	Y	SKIN	4	Week(s)
AGE DEFYING SERIES CREAM PACKETTE	CAP0893201		Unknown	Female Adult	28-Jan-00	TINGLING	US	N	SKIN	1	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0893294	34	Year(s)	Female Adult	28-Jan-00	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MEH0893269		Unknown	Female Adult	28-Jan-00	NAUSEA	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	SHE0893546		Unknown	Female Adult	31-Jan-00	TEARING	US	N	EYE INDIRECT	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ZIL0893391		Unknown	Female Adult	31-Jan-00	PIMPLES	US	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0893752	56	Year(s)	Female Adult	01-Feb-00	PIMPLES	US	N	SKIN	3	007
OLAY DAILY RENEWAL CREAM 2 OZ	HEF0893809		Unknown	Female Adult	01-Feb-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SWI0894083		Unknown	Female Adult	02-Feb-00	PIMPLES	US	N	SKIN	4	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GAR0894117		Unknown	Female Adult	03-Feb-00	RASH	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0894230		Unknown	Female Adult	03-Feb-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLA0894493		Unknown	Female Adult	04-Feb-00	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DRA0894521		Unknown	Female Adult	04-Feb-00	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RIT0894708	66	Year(s)	Female Adult	07-Feb-00	SWELLING	US	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRE0894777		Unknown	Female Adult	07-Feb-00	SWELLING	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CHA0895501		Unknown	Female Adult	10-Feb-00	REDNESS	US	N	SKIN	1	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOU0895321	39	Year(s)	Female Adult	10-Feb-00	SWELLING	CA	N	SKIN	4	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	MC 0896100	85	Year(s)	Female Adult	15-Feb-00	REDNESS	CA	N	SKIN	6	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HOG0896183	33	Year(s)	Female Adult	15-Feb-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	PIC0896106		Unknown	Female Adult	15-Feb-00	DRYNESS	US	N	SKIN	2	Week(s)

OLAY DAILY RENEWAL CREAM 2 OZ	WIL0896116		Unknown	Female Adult	15-Feb-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FEN0896292		Unknown	Female Adult	16-Feb-00	ACNE	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PHI0896509		Unknown	Female Adult	17-Feb-00	BURNING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	POP0897097		Unknown	Female Adult	22-Feb-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAI0897260	46	Year(s)	Female Adult	23-Feb-00	BLISTERS	US	N	SKIN	48	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LUB0897532		Unknown	Female Adult	24-Feb-00	SWELLING	US	N	SKIN	10	002
OLAY DAILY RENEWAL CREAM 2 OZ	CRA0897541		Unknown	Female Adult	25-Feb-00	BURNING	US	N	SKIN	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FIS0897551	41	Year(s)	Female Adult	25-Feb-00	RASH	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ROB0898004		Unknown	Female Adult	28-Feb-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEV0897969		Unknown	Female Adult	28-Feb-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ADA0898034	39	Year(s)	Female Adult	29-Feb-00	BUMPS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SIN0898272		Unknown	Female Adult	01-Mar-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	CRO0898487		Unknown	Female Adult	02-Mar-00	RASH	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAZ0898669		Unknown	Female Adult	03-Mar-00	PIMPLES	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	GOR0898783	72	Year(s)	Female Adult	06-Mar-00	BLISTERS	CA	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	JAC0898942	42	Year(s)	Female Adult	06-Mar-00	PIMPLES	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	OLS0898959	66	Year(s)	Female Adult	06-Mar-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WOS0899034		Unknown	Female Adult	06-Mar-00	RASH	US	Y	SKIN	9	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LAC0899407	55	Year(s)	Female Adult	08-Mar-00	BURNING	CA	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	RUT0899298	45	Year(s)	Female Adult	08-Mar-00	REDNESS	CA	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRU0899259		Unknown	Female Adult	08-Mar-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ENG0900063		Unknown	Female Adult	13-Mar-00	REDNESS	US	N	SKIN	7	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SMI0900159		Unknown	Female Adult	14-Mar-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SEN0900591	88	Year(s)	Female Adult	16-Mar-00	PIMPLES	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WIT0900535		Unknown	Female Adult	16-Mar-00	PIMPLES	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KAV0900968	57	Year(s)	Female Adult	20-Mar-00	SWELLING	US	N	SKIN	8	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KAV0900897		Unknown	004	20-Mar-00	SWELLING	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SWE0900892		Unknown	Female Adult	20-Mar-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CHI0901136		Unknown	Female Adult	21-Mar-00	RASH	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HEI0901110		Unknown	Unknown	21-Mar-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KRO0901568		Unknown	Female Adult	23-Mar-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0901587	38	Year(s)	Female Adult	23-Mar-00	BURNING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MC 0901536		Unknown	Female Adult	23-Mar-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NAT0901824	44	Year(s)	Female Adult	24-Mar-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MCK0901943	55	Year(s)	Female Adult	27-Mar-00	SWELLING	CA	N	SKIN	12	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MAC0901900	39	Year(s)	Female Adult	27-Mar-00	SWELLING	CA	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	THO0902203		Unknown	Female Adult	28-Mar-00	BURNING	US	N	SKIN	3	Day(s)

OLAY DAILY RENEWAL CREAM 2 OZ	WEI0902175		Unknown	Female Adult	28-Mar-00	SWELLING	CA	N	SKIN	12	Hour(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUC0902427		Unknown	Unknown	29-Mar-00	SORENESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	DAV0902391		Unknown	Female Adult	29-Mar-00	SWELLING	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	EKA0902444		Unknown	Female Adult	29-Mar-00	PIMPLES	US	N	SKIN	3	Months(s)
OLAY DAILY RENEWAL CREAM 2 OZ	FRA0902812		Unknown	Female Adult	31-Mar-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	TRO0902813		Unknown	Unknown	31-Mar-00	BURNING	US	N	SKIN	2	Day(s)
AGE DEFYING SERIES CREAM PACKETTE	MOO0902979	39	Year(s)	Female Adult	03-Apr-00	REDNESS	CA	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAR0903230	72	Year(s)	Female Adult	04-Apr-00	DISCOLORATION	US	N	SKIN		Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROG0903417		Unknown	Female Adult	05-Apr-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CO 0903749		Unknown	Female Adult	07-Apr-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	DYC0904097	23	Year(s)	Female Adult	10-Apr-00	BUMPS	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LAN0904414	68	Year(s)	Female Adult	12-Apr-00	REDNESS	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIT0905179		Unknown	Unknown	18-Apr-00	STINGING	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DUK0905354		Unknown	Unknown	19-Apr-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PAQ0905828		Unknown	Female Adult	24-Apr-00	REDNESS	CA	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HER0906019		Unknown	Unknown	25-Apr-00	IRRITATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SAL0905886		Unknown	Female Adult	25-Apr-00	TINGLING	US	N	EYE INDIRECT		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DAV0906134		Unknown	Female Adult	26-Apr-00	PIMPLES	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SEI0906052		Unknown	Female Adult	26-Apr-00	REDNESS	US	N	SKIN	2	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEA0906719	80	Year(s)	Female Adult	01-May-00	BURNING	US	N	SKIN	5	002
OLAY DAILY RENEWAL CREAM 2 OZ	ULE0906671	72	Year(s)	Female Adult	01-May-00	RUNNY NOSE	US	N	INHALATION	5	002
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	OET0906916	57	Year(s)	Female Adult	02-May-00	BURNING	US	N	SKIN	36	Hour(s)
OLAY DAILY RENEWAL CREAM 2 OZ	REN0906957	76	Year(s)	Female Adult	02-May-00	TEARING	US	N	EYE INDIRECT		Unknown
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0907292		Unknown	Female Adult	04-May-00	RASH	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BRA0907321		Unknown	Female Adult	04-May-00	REDNESS	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	LUD0907385		Unknown	Female Adult	04-May-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	IAC0907931		Unknown	Female Adult	10-May-00	SWELLING	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	HOR0908203		Unknown	Female Adult	11-May-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	MAN0908470	6	Unknown	Unknown	12-May-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	CAR0909340		Unknown	Female Adult	19-May-00	WELTS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	ROM0909262	49	Year(s)	Female Adult	19-May-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAB0910103		Unknown	Female Adult	25-May-00	REDNESS	US	N	SKIN	4	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	POO0910120	34	Year(s)	Female Adult	25-May-00	ITCHING	CA	N	SKIN	3	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0911064		Unknown	Female Adult	02-Jun-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BAA0911089		Unknown	Female Adult	02-Jun-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUL0911285	39	Year(s)	Female Adult	05-Jun-00	BLURRED VISION	US	N	EYE	20	002
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0911208		Unknown	Female Adult	05-Jun-00	WELTS	US	N	SKIN	1	Day(s)

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VON0911504		Unknown	Female Adult	06-Jun-00	REDNESS	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HAL0911465		Unknown	Female Adult	06-Jun-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PIT0911711		Unknown	Unknown	07-Jun-00	PIMPLES	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	CLI0911637		Unknown	Female Adult	07-Jun-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KIL0912325		Unknown	Female Adult	12-Jun-00	DRYNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MAY0912657		Unknown	Female Adult	14-Jun-00	PIMPLES	US	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAG0913032		Unknown	Female Adult	19-Jun-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WAT0913323		Unknown	Female Adult	21-Jun-00	SORENESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUR0913588	71	Year(s)	Unknown	23-Jun-00	TEARING	US	N	EYE INDIRECT	2	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	SOB0914105		Unknown	Female Adult	28-Jun-00	COUGHING	US	N	INHALATION		
OLAY DAILY RENEWAL CREAM 2 OZ	STA0914292		Unknown	Female Adult	29-Jun-00	REDNESS	US	N	SKIN		Unknown
OLAY DAILY RENEWAL CREAM 2 OZ	ACR0914388		Unknown	Female Adult	30-Jun-00	BURNING	US	N	EYE	5	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAN0914481	33	Year(s)	Female Adult	03-Jul-00	SWELLING	US	N	SKIN	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	NEK0914871		Unknown	Unknown	06-Jul-00	DRYNESS	US	N	SKIN	1	Week(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	REE0915150	16	Year(s)	004	10-Jul-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CAO0915316			Female Adult	11-Jul-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0916038			Unknown	19-Jul-00	REDNESS	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	COX0916223			Unknown	20-Jul-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BAN0917668	54	Year(s)	Female Adult	01-Aug-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GIL0917996	80	Year(s)	Female Adult	03-Aug-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	WAD0918604				09-Aug-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	WIL0919142			Unknown	14-Aug-00	BUMPS	US	N	SKIN		
OLAY ADS PROTECTIVE RENEWAL LOT PACKETTE	AUL0919417			Unknown	16-Aug-00	(GENERALIZED)	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STE0919550			Unknown	17-Aug-00	SORENESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	ART0919517			Unknown	17-Aug-00	DRYNESS	US	N	SKIN	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	BOY0920176			Unknown	23-Aug-00	REDNESS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0920443	58	Year(s)	Female Adult	24-Aug-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ASH0920976	81	Year(s)	Female Adult	29-Aug-00	IRRITATION	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KER0921039	58	Year(s)	Female Adult	29-Aug-00	PIMPLES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	KOB0921070			Unknown	29-Aug-00	HIVES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BLE0921176	54	Year(s)	Female Adult	30-Aug-00	BURNING	CA	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	DES0921883	70	Year(s)	Female Adult	06-Sep-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BRO0922341				11-Sep-00	WRINKLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	RAM0922576	42	Year(s)	Female Adult	12-Sep-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	PER0923865	58	Year(s)	Female Adult	21-Sep-00	BURNING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BRU0924730			Unknown	27-Sep-00	BUMPS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	FIE0926624			Unknown	09-Oct-00	BUMPS	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	UNK0926938			Unknown	11-Oct-00	SWELLING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BUC0926856	76	Year(s)	Female Adult	11-Oct-00	BURNING	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	GOR0926952	49	Year(s)	Female Adult	11-Oct-00	RASH	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JOH0927227				12-Oct-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MOY0928131			Unknown	18-Oct-00	RASH	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	VIE0928437			Unknown	20-Oct-00	REDNESS	US	N	SKIN	2	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	WAR0928423	52	Year(s)	Female Adult	20-Oct-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0929057			Unknown	24-Oct-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOL0929118	42	Year(s)	Female Adult	25-Oct-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PUE0929212			Unknown	25-Oct-00	PIMPLES	US	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	JON0930002			Unknown	31-Oct-00	TEARING	US	N	EYE INDIRECT	1	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	SCH0930122			Unknown	01-Nov-00	BUMPS	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	SNY0931424			Unknown	01-Nov-00	HIVES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HUF0930589	49	Year(s)	Female Adult	02-Nov-00	TEARING	US	N	EYE INDIRECT		
OLAY DAILY RENEWAL CREAM 2 OZ	MAR0930799	28	Year(s)	Female Adult	03-Nov-00	RASH	CA	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	MOO0930693	62	Year(s)	Female Adult	03-Nov-00	REDNESS	US	N	SKIN	1	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BOW0931988	54	Year(s)	Female Adult	10-Nov-00	DISCOLORATION	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	HOS0931991	63	Year(s)	Female Adult	10-Nov-00	IRRITATION	US	N	EYE INDIRECT	3	Day(s)
OLAY DAILY RENEWAL CREAM 2 OZ	MOR0932066	32	Year(s)	Female Adult	10-Nov-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	GRE0932240				13-Nov-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CRA0932605			Unknown	14-Nov-00	SORENESS	US	N	EYE		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	TAY0933324	69	Year(s)	Female Adult	20-Nov-00	TEARING	CA	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HEA0933617				21-Nov-00	SWELLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KIE0933632			Unknown	22-Nov-00	WARM/FLUSHED	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	ITU0934970	50	Second(s)	Unknown	04-Dec-00	REDNESS	CA	Y	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEN0934944				04-Dec-00	PIMPLES	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	PEN0934944				04-Dec-00	PIMPLES	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	BUF0935078	47	Year(s)	Female Adult	05-Dec-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	BUS0935131		Second(s)	Unknown	05-Dec-00	DRYNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAC0935360		Second(s)	Unknown	06-Dec-00	ITCHING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	LEE0935467			Unknown	07-Dec-00	TEARING	US	N	INHALATION		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MAR0935452		Second(s)	Unknown	07-Dec-00	STINGING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MC 0935473		Second(s)	Unknown	07-Dec-00	REDNESS	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HAR0935724			Unknown	08-Dec-00	RASH	US	N	SKIN	2	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	KRA0935690			Unknown	08-Dec-00	ALLERGIC REACTION	US	Y	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	CIA0935869		Second(s)	Unknown	11-Dec-00	REDNESS	US	N	SKIN	3	Day(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	JOH0935966	42	Year(s)	Female Adult	11-Dec-00	SWELLING	US	N	SKIN		

OLAY AGE DEFYING RENEWAL CREAM SIZE ND	HOW0936443	72	Year(s)	Female Adult	14-Dec-00	IRRITATION	US	N	SKIN	2	Months(s)
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	MUG0936360			Unknown	14-Dec-00	RASH	CA	N	SKIN	1	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	HAR0936687	43	Year(s)	Female Adult	18-Dec-00	REDNESS	US	N	EYE INDIRECT		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	NIE0937263	78	Year(s)	Female Adult	21-Dec-00	TINGLING	US	N	SKIN		
OLAY AGE DEFYING RENEWAL CREAM SIZE ND	STR0937714		Second(s)	Unknown	27-Dec-00	REDNESS	US	N	SKIN	3	Week(s)
OLAY DAILY RENEWAL CREAM 2 OZ	KEM0937660	63	Year(s)	Female Adult	27-Dec-00	RASH	US	N	SKIN		
OLAY DAILY RENEWAL CREAM 2 OZ	FLA0937912		Second(s)	Unknown	28-Dec-00	PEELING	US	N	SKIN	4	Day(s)

COMMENTS FOR CLEARASIL CLEARSTICK WITH SALICYLIC ACID

NA HEF Comments for [illegible]rsticks with Salicylic Acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	City	MD	Incident	Duration	Amount
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	UNK0715985		Unknown	Male Child	02-Jan-97	CRACKING	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	TAN0716171	15	Year(s)	Female Child	03-Jan-97	RASH	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	MC 0716433		Unknown	Male Adult	06-Jan-97	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	TAN0716281	16	Year(s)	Male Child	06-Jan-97	RASH	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	OSO0716990		Unknown	Female Child	09-Jan-97	STINGING/BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0717711	12	Year(s)	Female Child	14-Jan-97	WARM	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	TRE0718445		Unknown	Female Child	21-Jan-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	HAY0719076	15	Year(s)	Female Child	23-Jan-97	WELTS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ROS0719022		Unknown	Female Adult	23-Jan-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	QUA0719250	14	Year(s)	Female Child	24-Jan-97	PEELING	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	DEA0719726	22	Unknown	Male Adult	28-Jan-97	RASH	US	N	SKIN	48	Hour(s)
CLEARASIL CLEARSTICK ND	UNK0720546		Unknown	Female Adult	03-Feb-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	OLS0721166	14	Year(s)	Female Adult	06-Feb-97	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ZEO0721169	13	Year(s)	Unknown	06-Feb-97	ACNE	US	N	SKIN	2	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	ARC0721373	65	Year(s)	Female Adult	07-Feb-97	BUMPS	US	N	SKIN	1	Hour(s)
CLEARSTICK MAX 1.2 OZ	PER0721812	14	Year(s)	Female Adult	11-Feb-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	SHE0721960		Unknown	Female Adult	12-Feb-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	MIL0722204	13	Year(s)	Female Child	13-Feb-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SEE0722119	15	Year(s)	Unknown	13-Feb-97	PIMPLES	US	N	SKIN	1.5	Week(s)
CLEARASIL CLEARSTICK ND	SCO0722857		Unknown	Female Child	20-Feb-97	DRYNESS	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	HAE0724355	11	Year(s)	Female Child	03-Mar-97	CUT	US	N	INJURY		
CLEARSTICK MAX 1.2 OZ	GRU0724679	14	Unknown	Unknown	05-Mar-97	BUMPS	US	N	SKIN	20	Minute(s)
CLEARASIL CLEARSTICK SENS SKIN	OHN0725046		Unknown	Male Adult	07-Mar-97	ACNE	US	N	SKIN	14	Day(s)
CLEARSTICK MAX 1.2 OZ	WU0725368	12	Year(s)	Female Child	10-Mar-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	NEW0725928	12	Year(s)	Female Child	13-Mar-97	RASH	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	AAN0726619		Unknown	Female Adult	19-Mar-97	DRYNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SAN0726812	14	Year(s)	Female Adult	19-Mar-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	VAR0726699		Unknown	Female Child	19-Mar-97	ITCHING	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	ROM0726807	14	Year(s)	Female Child	19-Mar-97	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	AAN0726618		Unknown	Female Adult	19-Mar-97	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RON0726729		Unknown	Female Child	19-Mar-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK ND	WIL0727965		Unknown	Male Adult	27-Mar-97	PEELING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SCH0727855	22	Year(s)	Male Adult	27-Mar-97	ITCHING	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	RAT0728379		Unknown	Male Adult	01-Apr-97	ACNE	US	N	SKIN	2	Week(s)

DISC CLEARASIL CLEARSTICK MAXIMUM ND	MIL0728446	12	Year(s)	Female Child	01-Apr-97	DRYNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	STE0729399	15	Year(s)	Female Child	08-Apr-97	RASH	US	N	SKIN		Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MC 0729482		Unknown	Female Adult	09-Apr-97	ACNE	US	N	SKIN		
CLEARASIL CLEARSTICK SENSITIVE ND	MAT0729623	13	Year(s)	Female Child	09-Apr-97	DRYNESS	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	SOT0729538	18	Year(s)	Female Adult	09-Apr-97	ACNE	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	IRB0729952	13	Year(s)	Female Child	11-Apr-97	BURNING	US	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	FRO0731665	14	Year(s)	Female Child	23-Apr-97	BURNING	US	N	SKIN	10	Minute(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	BAZ0731615		Unknown	Female Adult	23-Apr-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRO0732233		Unknown	Female Adult	28-Apr-97	DRYNESS	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	BRA0732395	12	Year(s)	Female Child	29-Apr-97	BLEMISHES	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	KOE0732360		Unknown	Female Adult	29-Apr-97	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	MOR0732547		Unknown	Female Child	30-Apr-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LIM0733433		Unknown	Female Adult	07-May-97	PEELING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	COS0733947	17	Year(s)	Female Child	12-May-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	SHA0733949		Unknown	Unknown	12-May-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	JAC0734019		Unknown	Male Adult	13-May-97	ACNE	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	WIL0734157		Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GOL0734598		Unknown	Female Adult	16-May-97	IRRITATION	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	OTT0734492	13	Year(s)	Female Child	16-May-97	BUMPS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	KUS0734626	12	Year(s)	Female Child	19-May-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	GRE0734983	14	Year(s)	Female Child	20-May-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	EYM0735145	12	Year(s)	Male Child	20-May-97	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	DAR0735284		Unknown	Male Child	21-May-97	TINGLING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	BAZ0735329	36	Year(s)	Female Adult	22-May-97	REDNESS	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	VIL0735636	14	Year(s)	Female Child	23-May-97	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	JOL0735760		Unknown	Male Adult	27-May-97	ITCHING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0736188	13	Year(s)	Female Child	29-May-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0736812	13	Year(s)	Female Child	03-Jun-97	BURNING	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	MCK0736983		Unknown	Female Adult	04-Jun-97	WELTS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	RIC0737357	21	Year(s)	Male Adult	06-Jun-97	REDNESS	US	N	SKIN	4	Unknown
CLEARSTICK MAX 1.2 OZ	ROL0737250	14	Year(s)	Female Child	06-Jun-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	ORR0737511	33	Year(s)	Female Adult	09-Jun-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	PAR0737922	14	Year(s)	Female Child	11-Jun-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	POR0737960	13	Year(s)	Female Child	11-Jun-97	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	GAR0737816	13	Unknown	Female Child	11-Jun-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	AWA0738323	14	Year(s)	Male Child	13-Jun-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRO0738624		Unknown	Female Child	17-Jun-97	BURNING	US	N	SKIN		

CLEARSTICK MAX 1.2 OZ	CAS0739906	34	Year(s)	Male Adult	25-Jun-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	HAY0740125		Unknown	Female Child	26-Jun-97	PEELING	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENSITIVE ND	SIM0740746	16	Year(s)	Male Child	01-Jul-97	CRAMPING	US	N	N		
CLEARSTICK MAX 1.2 OZ	BON0740674	12	Year(s)	Female Child	01-Jul-97	STINGING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	DEG0741377	11	Year(s)	Female Child	07-Jul-97	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	GOH0741512	15	Year(s)	Male Child	08-Jul-97	STINGING	US	N	SKIN	15	Minute(s)
CLEARSTICK MAX 1.2 OZ	FRE0741531	16	Unknown	Female Child	08-Jul-97	RASH	US	N	SKIN	6	Hour(s)
CLEARSTICK MAX 1.2 OZ	RAN0742322	13	Year(s)	Male Child	14-Jul-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	HAN0742441		Unknown	Female Child	15-Jul-97	PEELING	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	PAP0742717	15	Year(s)	Male Child	16-Jul-97	BURNING	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	REF0742745		Unknown	Female Child	16-Jul-97	BURNING	US	N	EYE		
CLEARASIL CLEARSTICK SENS SKIN	PER0742883	14	Year(s)	Female Child	17-Jul-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	VAN0742782	14	Year(s)	Female Child	17-Jul-97	OTHER	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	BOW0742816	14	Year(s)	Male Child	17-Jul-97	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MUR0742801	2	Year(s)	Female Child	17-Jul-97	NONE	US	N	N		
CLEARASIL CLEARSTICK SENS SKIN	GUE0742965	12	Year(s)	Female Child	18-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	HAN0743017	15	Year(s)	Female Adult	18-Jul-97	STINGING	US	N	SKIN	4	Minute(s)
CLEARSTICK MAX 1.2 OZ	PER0742976		Unknown	Female Adult	18-Jul-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	WIR0743219	19	Year(s)	Male Adult	21-Jul-97	IRRITATION	US	N	EYE	1	Hour(s)
CLEARASIL CLEARSTICK ND	BAN0744051		Unknown	Female Adult	25-Jul-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BLE0744792		Unknown	Female Child	31-Jul-97	PIMPLES	US	N	SKIN	1	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	PIE0745379	13	Year(s)	Female Child	04-Aug-97	ACNE	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SAN0745376		Unknown	Female Child	04-Aug-97	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	JON0745912	17	Unknown	Female Adult	07-Aug-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK ND	MAC0746588	19	Year(s)	Male Adult	12-Aug-97	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	UNK0747110		Unknown	Female Child	15-Aug-97	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BEL0747738	13	Year(s)	Unknown	20-Aug-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAR0747870	18	Year(s)	Female Adult	20-Aug-97	IRRITATION	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MON0749361		Unknown	Female Adult	02-Sep-97	RASH	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	MED0749873	15	Year(s)	Male Adult	03-Sep-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	RUS0750184	13	Year(s)	Female Adult	05-Sep-97	PEELING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	NGU0750564	13	Year(s)	Female Child	08-Sep-97	BUMPS	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	CHA0751179		Unknown	Unknown	11-Sep-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0751330	13	Year(s)	Unknown	12-Sep-97	DRYNESS	US	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	POR0751845	2	Year(s)	Male Child	16-Sep-97	NONE	CA	N	N		
CLR CST TRT REG ST NTNT 1.2 OZ	SAN0752493	41	Year(s)	Female Adult	19-Sep-97	DRYNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	KEN0753153	16	Year(s)	Female Child	23-Sep-97	BLISTERS	US	N	SKIN	1	Day(s)

CLEARSTICK MAX 1.2 OZ	MAR0753035	16	Year(s)	Female Child	23-Sep-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PRI0753414	19	Year(s)	Male Adult	24-Sep-97	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	LO 0753635	30	Year(s)	Female Adult	26-Sep-97	RASH	CA	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	OVE0754101	19	Year(s)	Female Adult	29-Sep-97	INFLAMED	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK ND	PER0755269	18	Year(s)	Male Adult	06-Oct-97	BLISTERS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	KLA0755012	13	Year(s)	Male Child	06-Oct-97	STINGING	CA	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	KON0755124	19	Year(s)	Female Adult	06-Oct-97	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	VEL0755501		Unknown	Male Child	07-Oct-97	RASH	US	N	SKIN		
CLEARASIL CLEARSTICK ND	REF0755792		Unknown	Female Adult	08-Oct-97	NONE	US	N	N		
CLEARASIL CLEARSTICK SENS SKIN	BRO0755759	12	Year(s)	Female Adult	08-Oct-97	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BEC0755762	14	Year(s)	Male Child	08-Oct-97	IRRITATION	US	N	EYE	2	Hour(s)
CLEARSTICK MAX 1.2 OZ	LIN0756742	13	Year(s)	Female Child	14-Oct-97	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RIO0756846		Unknown	Female Adult	15-Oct-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	SCO0758022	14	Year(s)	Female Child	21-Oct-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	DUB0758667	11	Year(s)	Female Child	24-Oct-97	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	RUS0759881	14	Year(s)	Female Child	31-Oct-97	IRRITATION	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	WIL0759917	17	Year(s)	Male Child	31-Oct-97	SORENESS	US	N	N	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	FEN0760495	12	Year(s)	Female Child	04-Nov-97	SWELLING	US	N	SKIN	12	Hour(s)
CLEARASIL CLEARSTICK SENS SKIN	UNK0761070	13	Year(s)	Female Child	07-Nov-97	PEELING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	JOH0761145		Unknown	Female Adult	07-Nov-97	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	LAN0761738	55	Year(s)	Male Adult	11-Nov-97	SWELLING	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	ROD0761788	15	Year(s)	Unknown	11-Nov-97	PIMPLES	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	REF0762261	13	Year(s)	Female Child	13-Nov-97	FLAKING	CA	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	WHE0762710	4	Year(s)	Male Child	17-Nov-97	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	RHY0763132	14	Year(s)	Female Child	18-Nov-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	COO0763391	15	Year(s)	Female Child	19-Nov-97	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	WIL0764090		Unknown	Male Adult	24-Nov-97	REDNESS	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK SENS SKIN	MC 0764409	11	Year(s)	Female Adult	25-Nov-97	REDNESS	US	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	CHA0765647	3	Year(s)	Male Child	03-Dec-97	SWELLING/INFLAMED	US	N	N		Unknown
CLEARSTICK MAX 1.2 OZ	GRI0766633	32	Year(s)	Female Adult	09-Dec-97	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	DAB0767560	13	Year(s)	Female Child	15-Dec-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	COL0769686	15	Unknown	Female Child	31-Dec-97	RASH	US	Y	SKIN		
CLEARSTICK MAX 1.2 OZ	BAR0770263	12	Year(s)	Unknown	05-Jan-98	BURNING	US	N	SKIN	5	Minute(s)
CLEARSTICK MAX 1.2 OZ	PAP0770852	16	Year(s)	Female Child	07-Jan-98	ACNE	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	PER0770814	16	Year(s)	Unknown	07-Jan-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	POP0770850		Unknown	Unknown	07-Jan-98	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	LIN0771069		Unknown	Female Adult	08-Jan-98	ACNE	US	N	SKIN		Unknown

CLEARSTICK MAX 1.2 OZ	PAP0771073	17	Year(s)	Female Child	08-Jan-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SPE0771062	14	Year(s)	Male Child	08-Jan-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	HOW0771332	12	Year(s)	Female Child	09-Jan-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	LOP0771903	15	Year(s)	Male Child	13-Jan-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	POP0772869	16	Year(s)	Female Adult	20-Jan-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	BAR0773638	15	Year(s)	Male Child	23-Jan-98	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GAR0773818	18	Year(s)	Female Adult	26-Jan-98	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	AHL0774230		Unknown	Male Adult	27-Jan-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	ZER0774827		Unknown	Unknown	29-Jan-98	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	MOS0775645	16	Year(s)	Female Adult	03-Feb-98	PIMPLES	US	N	SKIN	7	Day(s)
CLEARSTICK MAX 1.2 OZ	DAV0776064		Unknown	Female Adult	06-Feb-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WON0776772		Unknown	Female Adult	10-Feb-98	IRRITATION	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RUI0777116	13	Year(s)	Female Child	11-Feb-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	BOW0777792	16	Year(s)	Female Child	17-Feb-98	RASH	US	N	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	WOO0777897	13	Year(s)	Female Child	17-Feb-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	FEE0778575		Unknown	Female Adult	20-Feb-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	NGU0779323		Unknown	Female Adult	25-Feb-98	PIMPLES	US	N	SKIN		Unknown
CLEARASIL CLEARSTICK ND	SCH0779672	14	Year(s)	Female Child	26-Feb-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	COW0780097	53	Year(s)	Male Adult	02-Mar-98	REDNESS	US	N	SKIN	6	Hour(s)
CLEARSTICK MAX 1.2 OZ	VLA0780051		Unknown	Female Adult	02-Mar-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WOR0780188	13	Unknown	Female Adult	02-Mar-98	RASH	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	GOR0780756		Unknown	Unknown	04-Mar-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PER0780762		Unknown	Male Adult	04-Mar-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	NO 0781580		Unknown	Female Adult	09-Mar-98	RASH	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	HAY0782101	43	Year(s)	Female Adult	11-Mar-98	REDNESS	US	N	SKIN	2	Day(s)
CLR CST TRT REG ST NTNT 1.2 OZ	CAN0781879	20	Year(s)	Female Adult	11-Mar-98	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	VAR0783216		Unknown	Female Adult	17-Mar-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ALE0783574		Unknown	Female Adult	18-Mar-98	ACNE	US	Y	SKIN	2	Week(s)
CLEARASIL CLEARSTICK ND	THO0784407		Unknown	Unknown	23-Mar-98	IRRITATION	CA	N	SKIN	1	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	BER0784314	12	Year(s)	Female Child	23-Mar-98	STINGING	CA	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SAR0784894		Unknown	Male Adult	25-Mar-98	DISCOLORATION	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	LUC0786015	11	Year(s)	Female Child	01-Apr-98	STINGING	US	N	SKIN	5	Minute(s)
CLEARSTICK MAX 1.2 OZ	TIE0787306	13	Year(s)	Female Child	08-Apr-98	BUMPS	US	N	SKIN		Unknown
CLEARSTICK MAX 1.2 OZ	ORT0787743	15	Year(s)	Male Adult	13-Apr-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WHI0789964		Unknown	Female Adult	23-Apr-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FAR0790190	13	Year(s)	Male Child	24-Apr-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	TIE0790358	18	Year(s)	Female Adult	27-Apr-98	REDNESS	CA	N	SKIN	3	Week(s)

CLEARSTICK MAX 1.2 OZ	RAW0791661		Unknown	Male Adult	04-May-98	SWELLING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	WIL0791826	13	Year(s)	Male Child	04-May-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LAN0792032	38	Year(s)	Female Adult	05-May-98	REDNESS	CA	N	SKIN	4	Hour(s)
CLEARSTICK MAX 1.2 OZ	TES0792728	17	Year(s)	Male Child	08-May-98	ACNE	US	N	SKIN	10	Day(s)
CLEARSTICK MAX 1.2 OZ	VED0792685		Unknown	Female Adult	08-May-98	PIMPLES	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	TOR0793226	12	Year(s)	Female Adult	12-May-98	PEELING	US	Y	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	GUR0794679	30	Year(s)	Female Adult	21-May-98	ACNE	CA	N	SKIN	1	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	STE0794923	15	Year(s)	Female Child	25-May-98	REDNESS	CA	Y	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	ALI0795548	20	Year(s)	Female Adult	28-May-98	BURNING	CA	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GOO0796703	14	Year(s)	Male Child	04-Jun-98	RASH	US	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK ND	COL0796837	10	Year(s)	Unknown	05-Jun-98	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	HAM0797018	15	Year(s)	Female Adult	08-Jun-98	BUMPS	US	N	SKIN	2	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	PRO0799252	33	Year(s)	Female Adult	22-Jun-98	BURNING	CA	N	SKIN	5	Minute(s)
CLEARASIL CLEARSTICK SENS SKIN	COU0800150	13	Unknown	Female Child	25-Jun-98	SWELLING	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	COU0801087	16	Year(s)	Female Child	01-Jul-98	RASH	US	N	SKIN	10	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	GER0801540	12	Year(s)	Female Child	06-Jul-98	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	RHO0801722	13	Year(s)	Female Child	06-Jul-98	PIMPLES	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	NIC0801620	19	Unknown	Female Adult	06-Jul-98	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	OLL0802069	46	Year(s)	Female Adult	08-Jul-98	BURNING	CA	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAD0802120	13	Year(s)	Female Child	08-Jul-98	ACNE	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	SMI0802235	15	Year(s)	Female Child	08-Jul-98	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	HUD0802329		Unknown	Unknown	09-Jul-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	BUR0802792	15	Year(s)	Female Child	10-Jul-98	REDNESS	US	N	SKIN	1	Day(s)
CLEARSTICK MAX 1.2 OZ	ZOR0802730	14	Year(s)	Male Child	10-Jul-98	RASH	US	N	SKIN	2	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	RIC0804385	12	Year(s)	Female Child	20-Jul-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SAX0804980	16	Year(s)	Female Child	22-Jul-98	RASH	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	BAR0805297	41	Year(s)	Female Adult	23-Jul-98	ACNE	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	BEL0805143	37	Year(s)	Female Adult	23-Jul-98	ITCHING	US	N	SKIN	24	Hour(s)
CLEARSTICK MAX 1.2 OZ	MAD0805250	14	Year(s)	Unknown	23-Jul-98	STINGING	US	N	SKIN	1	Month(s)
CLR CST TRT REG ST NTNT 1.2 OZ	JAC0805077	24	Year(s)	Female Adult	23-Jul-98	BURNING	CA	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	BAR0805737	16	Year(s)	Female Child	27-Jul-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	MAL0805596		Unknown	Female Adult	27-Jul-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PEA0805965	12	Unknown	Female Child	27-Jul-98	BLEMISHES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	BRO0806709	17	Year(s)	Female Child	30-Jul-98	SWELLING	US	N	SKIN		Minute(s)
CLEARSTICK MAX 1.2 OZ	HAM0806966	16	Year(s)	Unknown	31-Jul-98	PIMPLES	US	N	SKIN	8	Day(s)
CLEARSTICK MAX 1.2 OZ	DAV0807131	13	Year(s)	Female Child	03-Aug-98	STINGING	US	N	SKIN	30	Second(s)
CLEARASIL CLEARSTICK ND	RAN0807700		Unknown	Female Adult	05-Aug-98	PIMPLES	CA	N	SKIN		Unknown

CLEARASIL CLEARSTICK SENS SKIN	JON0808077	38	Year(s)	Female Adult	06-Aug-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FRY0807912	21	Year(s)	Female Adult	06-Aug-98	STINGING	US	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	FLO0809194		Unknown	Male Adult	13-Aug-98	PEELING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	CIR0810457	19	Year(s)	Female Adult	19-Aug-98	(GENERALIZED)	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BIE0810376	15	Year(s)	Female Child	19-Aug-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MAR0811564		Unknown	Female Adult	26-Aug-98	OTHER	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	PAR0811938	15	Year(s)	Male Child	28-Aug-98	BURNING	CA	N	SKIN	2	Minute(s)
CLEARSTICK MAX 1.2 OZ	BRI0811993		Unknown	Male Adult	28-Aug-98	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	WAT0812364	13	Year(s)	Female Child	31-Aug-98	HIVES	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	TRE0813001	21	Year(s)	Female Adult	03-Sep-98	BURNING	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	GRO0814533		Unknown	Female Adult	15-Sep-98	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	TRE0815223	13	Year(s)	Male Child	18-Sep-98	PEELING	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	HIR0816122		Unknown	Female Adult	25-Sep-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SIL0816637	15	Year(s)	Male Child	29-Sep-98	REDNESS	CA	Y	SKIN		
CLEARSTICK MAX 1.2 OZ	LA 0817607	12	Year(s)	Female Child	05-Oct-98	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	PER0818014	15	Year(s)	Female Child	07-Oct-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SES0817984	18	Year(s)	Female Child	07-Oct-98	PIMPLES	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	UNK0817996	18	Year(s)	Female Child	07-Oct-98	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK ND	NEL0818208		Unknown	Female Adult	08-Oct-98	ACNE	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	KEN0819493	14	Year(s)	Unknown	16-Oct-98	RASH	US	N	SKIN	1	Month(s)
CLEARSTICK MAX 1.2 OZ	KEM0820188	16	Year(s)	Male Child	21-Oct-98	BURNING	CA	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	COR0822340	13	Year(s)	Male Adult	03-Nov-98	BLEEDING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MC 0823329	33	Year(s)	Female Adult	09-Nov-98	ACNE	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	CAL0823537		Unknown	Female Adult	10-Nov-98	BURNING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	MAL0823490	22	Year(s)	Male Adult	10-Nov-98	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ODO0824817	13	Year(s)	Male Child	17-Nov-98	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	SAN0826606	13	Year(s)	Female Adult	30-Nov-98	HIVES	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	REF0826432	35	Year(s)	Female Adult	30-Nov-98	REDNESS	CA	N	SKIN	3	007
CLEARSTICK MAX 1.2 OZ	REF0826432	35	Year(s)	Female Adult	30-Nov-98	REDNESS	CA	N	SKIN	3	007
CLEARSTICK MAX 1.2 OZ	BLA0826777	13	Unknown	Male Child	01-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	SCO0827018	20	Year(s)	Female Adult	02-Dec-98	PIMPLES	US	N	SKIN	1	Week(s)
CLEARSTICK MAX 1.2 OZ	JON0828339		Unknown	Unknown	10-Dec-98	SWELLING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	YOS0828693	16	Year(s)	Female Child	14-Dec-98	TEARING	US	N	EYE	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	VIT0830142	14	Year(s)	Female Child	22-Dec-98	REDNESS	US	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	BEL0830947		Unknown	Male Child	30-Dec-98	STINGING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	SMI0831054	23	Year(s)	Female Adult	30-Dec-98	REDNESS	US	N	SKIN	1	Week(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	DUJ0835784	14	Year(s)	Female Child	28-Jan-99	ACNE	CA	N	SKIN	2	Day(s)

CLEARSTICK MAX 1.2 OZ	SHU0839052	15	Year(s)	Male Adult	17-Feb-99	PIMPLES	US	N	SKIN		Day(s)
CLEARSTICK MAX 1.2 OZ	JEW0839147		Unknown	Female Adult	18-Feb-99	REDNESS	US	N	SKIN		
DISC CLEARASIL CLEARSTICK MAXIMUM ND	GAR0839854	13	Year(s)	Female Child	22-Feb-99	STINGING	US	N	SKIN	3	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	KIN0840890	15	Year(s)	Female Adult	26-Feb-99	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MOR0841993		Unknown	Female Adult	04-Mar-99	SWELLING	US	N	SKIN	2	Day(s)
CLEARSTICK MAX 1.2 OZ	LOG0842310	13	Year(s)	Female Child	05-Mar-99	REDNESS	US	N	SKIN	7	Hour(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	EDW0842168		Unknown	Female Adult	05-Mar-99	BURNING	US	N	SKIN	2	Minute(s)
CLEARSTICK MAX 1.2 OZ	HER0842737	33	Year(s)	Female Adult	08-Mar-99	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	REF0843654		Unknown	Unknown	12-Mar-99	STINGING	US	N	SKIN		
CLEARASIL CLEARSTICK SENS SKIN	WOL0845747		Unknown	Male Adult	23-Mar-99	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	RUB0847541		Unknown	Male Adult	01-Apr-99	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MET0848570	19	Year(s)	Female Adult	08-Apr-99	BURNING	US	N	SKIN	1	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	SEC0849152	10	Year(s)	Male Child	12-Apr-99	SWELLING	US	N	SKIN	5	Day(s)
CLR CST TRT REG ST NTNT 1.2 OZ	SIC0849127	11	Year(s)	Male Child	12-Apr-99	RASH	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	MIC0849363		Unknown	Female Adult	13-Apr-99	SORENESS	US	N	SKIN	1	Day(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	AND0850573		Unknown	Male Adult	19-Apr-99	BURNING	US	N	SKIN	1	Week(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	GUD0850586	13	Year(s)	Male Child	19-Apr-99	ITCHING	US	N	SKIN	4	Day(s)
DISC CLEARASIL CLEARSTICK MAXIMUM ND	BAN0851561	2	Year(s)	Male Child	26-Apr-99	NONE	US	N	N		
CLEARSTICK MAX 1.2 OZ	YAN0852146		Unknown	Unknown	28-Apr-99	ITCHING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	SAN0852968	16	Year(s)	Female Adult	03-May-99	DISCOLORATION	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	SUA0854488	13	Year(s)	Male Child	11-May-99	PEELING	US	N	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	UNK0854344		Unknown	Female Child	11-May-99	BURNING	US	N	SKIN	10	Minute(s)
CLEARSTICK MAX 1.2 OZ	MAX0855686		Unknown	Female Child	18-May-99	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ADA0856898		Unknown	Female Adult	25-May-99	PIMPLES	US	Y	SKIN	3	Day(s)
CLEARSTICK MAX 1.2 OZ	CAR0856906	16	Year(s)	Male Child	25-May-99	SWELLING	US	N	SKIN	1	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	CRU0858768		Unknown	Male Adult	04-Jun-99	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK ND	GON0859031		Unknown	Unknown	07-Jun-99	PIMPLES	US	N	SKIN	3	Week(s)
CLR CST TRT REG ST NTNT 1.2 OZ	LUC0859971	29	Year(s)	Male Adult	14-Jun-99	PIMPLES	CA	N	SKIN	12	Hour(s)
CLEARSTICK MAX 1.2 OZ	REF0864575		Unknown	Male Adult	12-Jul-99	PIMPLES	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	FES0864728	15	Year(s)	Female Child	13-Jul-99	BURNING	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	HIC0864779	18	Year(s)	Female Adult	13-Jul-99	BUMPS	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	MCA0866143	14	Year(s)	Female Adult	21-Jul-99	RASH	CA	N	SKIN	2	Week(s)
CLEARASIL CLEARSTICK SENS SKIN	LAW0866728	12	Year(s)	Female Child	26-Jul-99	ACNE	US	N	SKIN	2	Week(s)
CLEARSTICK MAX 1.2 OZ	COL0871107	13	Year(s)	Female Child	24-Aug-99	ACNE	US	Y	SKIN		
CLEARASIL CLEARSTICK ND	DAV0871883	15	Year(s)	Male Child	30-Aug-99	BURNING	US	N	SKIN	4	Minute(s)
CLEARSTICK MAX 1.2 OZ	HAS0873537	21	Year(s)	Male Adult	09-Sep-99	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BUT0873739	25	Year(s)	Female Child	10-Sep-99	PIMPLES	US	N	SKIN	2	Day(s)

CLEARSTICK MAX 1.2 OZ	SMI0876377		Unknown	Unknown	28-Sep-99	RASH	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	ADE0876885		Unknown	Female Adult	01-Oct-99	DRYNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BAK0877485	27	Year(s)	Female Adult	06-Oct-99	REDNESS	US	N	SKIN	4	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	SCO0883283		Unknown	Female Adult	12-Nov-99	DRYNESS	US	N	SKIN	3	Week(s)
CLEARSTICK MAX 1.2 OZ	SCO0883282		Unknown	Female Adult	12-Nov-99	DRYNESS	US	N	SKIN	3	Week(s)
CLEARASIL CLEARSTICK ND	YAN0883847	30	Year(s)	Female Adult	16-Nov-99	REDNESS	CA	N	SKIN	5	Day(s)
CLEARASIL CLEARSTICK REGULAR ND	GAR0885111		Unknown	Female Adult	26-Nov-99	RASH	CA	N	SKIN	3	Day(s)
CLEARASIL CLEARSTICK SENS SKIN	EGA0895244	13	Year(s)	Male Child	09-Feb-00	DISCOLORATION	CA	N	SKIN	8	Hour(s)
CLEARASIL CLEARSTICK ND	POO0895856	16	Year(s)	Male Child	14-Feb-00	IRRITATION	CA	N	EYE	5	Minute(s)
CLEARASIL CLEARSTICK ND	DEA0897856		Unknown	Female Adult	28-Feb-00	RASH	US	N	SKIN	36	Hour(s)
CLR CST TRT REG ST NTNT 1.2 OZ	BAR0901284		Unknown	Female Child	21-Mar-00	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	KAU0901929	20	Year(s)	Female Adult	27-Mar-00	BURNING	CA	N	SKIN	5	Minute(s)
CLEARASIL CLEARSTICK ND	UNK0905799		Unknown	Unknown	24-Apr-00	BUMPS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	SCO0909301	15	Year(s)	Female Child	19-May-00	RASH	US	N	SKIN	3	Month(s)
CLEARASIL CLEARSTICK SENS SKIN	GAL0911185	32	Year(s)	Female Adult	05-Jun-00	REDNESS	CA	N	SKIN	5	Day(s)
CLEARSTICK MAX 1.2 OZ	KES0911397	20	Unknown	Female Adult	05-Jun-00	RASH	US	N	SKIN	8	Hour(s)
CLEARSTICK MAX 1.2 OZ	FAT0911578		Unknown	Unknown	06-Jun-00	BURNING	US	N	SKIN		
CLEARASIL CLEARSTICK ND	OSE0913983	17	Year(s)	Female Child	27-Jun-00	REDNESS	CA	N	SKIN	5	Minute(s)
DISCONTINUED CLEARASIL CLEARSTICK ND	LAW0915839	13	Year(s)	Female Child	17-Jul-00	REDNESS	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	BRY0915982	13	Year(s)	Female Child	18-Jul-00	HEADACHE	US	N	ON		
CLEARASIL CLEARSTICK ND	HAR0919844			Unknown	21-Aug-00	BURNING	US	N	SKIN		
CLEARSTICK MAX 1.2 OZ	MOR0920527	50	Year(s)	Female Adult	25-Aug-00	SWELLING	US	Y	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	SPE0922435			Unknown	11-Sep-00	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	FAU0925172	14	Year(s)	Male Child	29-Sep-00	IRRITATION	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	WIL0933771			Unknown	22-Nov-00	BURNING	US	N	SKIN		
DISC CLEARASIL CLEARSTICK MAXIMUM ND	ALL0934803	24	Year(s)	Female Adult	01-Dec-00	REDNESS	US	N	SKIN		
CLEARASIL CLEARSTICK ND	FLO0935435	16	Year(s)	Female Child	06-Dec-00	BURNING	US	N	EYE		
CLEARASIL CLEARSTICK SENS SKIN	BOL0935938			Unknown	11-Dec-00	REDNESS	CA	N	SKIN		
CLEARASIL CLEARSTICK REGULAR ND	SAR0936080			Unknown	12-Dec-00	PIMPLES	US	N	SKIN		
CLEARASIL CLEARSTICK ND	PIZ0937262			Unknown	21-Dec-00	PIMPLES	US	N	SKIN		
CLR CST TRT REG ST NTNT 1.2 OZ	ST 0937386			Unknown	21-Dec-00	STINGING	CA	N	SKIN		

COMMENTS FOR CLEARASIL PADS WITH SALICYLIC ACID

NA HEF Comments for C[illegible]asil Pads with Salicylic Acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Ctry	MD	Incident	Duration	Amount
CLEARASIL PADS MAXIMUM 50 COUNT	HOG0716703		Unknown	Female Adult	08-Jan-97	RASH	US	N	SKIN	2	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MAC0716760		Unknown	Female Child	08-Jan-97	BUMPS	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	FRY0717037	16	Year(s)	Male Adult	09-Jan-97	STINGING/BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KIV0717273	14	Year(s)	Male Adult	13-Jan-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SMI0717330		Unknown	Female Adult	13-Jan-97	CRACKING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	JOS0717856		Unknown	Female Adult	15-Jan-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OLS0718326	18	Year(s)	Female Adult	17-Jan-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TOR0718591	12	Year(s)	Female Child	21-Jan-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	FIG0718654	15	Year(s)	Female Child	22-Jan-97	SORENESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KEL0718813	12	Year(s)	Female Child	22-Jan-97	RASH	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JOH0719222	15	Year(s)	Male Adult	24-Jan-97	PIMPLES	US	N	SKIN	3	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	COL0719665		Unknown	Male Child	28-Jan-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	OSB0719837		Unknown	Female Adult	29-Jan-97	BUMPS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ARN0720107	14	Unknown	Male Adult	30-Jan-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KAN0720388	17	Year(s)	Female Child	31-Jan-97	BUMPS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NUD0720336		Unknown	Male Adult	31-Jan-97	ACNE	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	TOL0720544	31	Year(s)	Female Adult	03-Feb-97	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	HIR0721043	16	Year(s)	Female Child	05-Feb-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	TOR0720967	14	Year(s)	Female Child	05-Feb-97	ITCHING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	DIS0721325	13	Year(s)	Female Child	07-Feb-97	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	CAR0721578		Unknown	Female Child	10-Feb-97	PIMPLES	US	N	SKIN	6	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEN0721535	21	Year(s)	Female Adult	10-Feb-97	REDNESS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NEA0721621	11	Year(s)	Female Child	10-Feb-97	BUMPS	US	N	SKIN	5	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SAB0721585	13	Year(s)	Female Child	10-Feb-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ADA0722193		Unknown	Female Adult	13-Feb-97	PIMPLES	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	AQT0722122	18	Year(s)	Female Adult	13-Feb-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	GON0722164	12	Year(s)	Female Child	13-Feb-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MOR0722201		Unknown	Female Child	13-Feb-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ORT0722964	12	Year(s)	Female Child	20-Feb-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	REY0723203	24	Year(s)	Female Adult	21-Feb-97	BUMPS	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	HOO0723878	16	Year(s)	Female Child	26-Feb-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MC 0724025	17	Year(s)	Male Adult	27-Feb-97	PIMPLES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	COL0724117	18	Year(s)	Unknown	28-Feb-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KIL0724410	25	Year(s)	Male Adult	03-Mar-97	BURNING	US	N	SKIN	20	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LA 0725157	13	Year(s)	Female Child	10-Mar-97	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ESA0725947		Unknown	Female Adult	14-Mar-97	BLISTERS	US	N	SKIN		

CLEARASIL PADS MAXIMUM 50 COUNT	ADA0726559	14	Year(s)	Male Adult	18-Mar-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OAK0726809	27	Year(s)	Female Adult	19-Mar-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	FAR0726748		Unknown	Male Adult	19-Mar-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	HAL0726918	15	Year(s)	Unknown	20-Mar-97	RASH	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JON0727639	13	Year(s)	Male Child	25-Mar-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	NIB0727743	13	Year(s)	Male Child	26-Mar-97	SCRATCH	US	N	INJURY		
CLEARASIL PADS MAXIMUM 50 COUNT	GIL0728258	12	Year(s)	Male Child	31-Mar-97	RASH	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DAR0728278	14	Year(s)	Male Child	01-Apr-97	ACNE	US	N	SKIN	3	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JEW0729210		Unknown	Female Child	07-Apr-97	REDNESS	US	N	SKIN	8	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KAH0729311	16	Year(s)	Unknown	08-Apr-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAX NTNT 40 COUNT	ADA0729794		Unknown	Female Adult	10-Apr-97	PIMPLES	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	FIN0729675	13	Year(s)	Unknown	10-Apr-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAT0729710		Unknown	Female Adult	10-Apr-97	IRRITATION	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KOE0730444	12	Year(s)	Unknown	15-Apr-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAN0730392	15	Year(s)	Female Child	15-Apr-97	REDNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LIE0730611	12	Year(s)	Female Child	16-Apr-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	BOO0730991	15	Year(s)	Female Child	18-Apr-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEE0731142		Unknown	Female Adult	21-Apr-97	RASH	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TRE0731254	22	Year(s)	Female Adult	21-Apr-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MOG0731409	15	Unknown	Male Child	22-Apr-97	DRYNESS	US	N	SKIN	4	Week(s)
CLEARASIL PADS ND	REF0732554		Unknown	Female Child	30-Apr-97	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	RIE0733129	12	Year(s)	Female Child	05-May-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	PHO0733303	14	Year(s)	Female Child	06-May-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BRA0734108	16	Year(s)	Male Adult	13-May-97	RASH	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BUR0734184	11	Year(s)	Male Child	13-May-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SAN0734089		Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	6	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	HOR0734552	21	Year(s)	Male Adult	16-May-97	BUMPS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	GUT0734608	16	Year(s)	Female Child	16-May-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	UNK0734555		Unknown	Unknown	16-May-97	REDNESS	US	N	EYE	5	Minute(s)
CLEARASIL PADS ND	WEL0734407		Unknown	Female Adult	16-May-97	DRYNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	OZA0734906		Unknown	Female Adult	19-May-97	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KOS0735614	12	Year(s)	Unknown	23-May-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	COO0736065	15	Year(s)	Female Child	28-May-97	DISCOLORATION	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DEL0735974	41	Year(s)	Male Adult	28-May-97	RUNNY NOSE	US	N	ON		
CLEARASIL PADS MAXIMUM 50 COUNT	BOS0736265	16	Year(s)	Male Child	29-May-97	PIMPLES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	UNG0736224		Unknown	Female Child	29-May-97	STINGING	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BLA0736431	27	Year(s)	Female Adult	30-May-97	RASH	US	N	SKIN	1	Day(s)

CLEARASIL PADS MAXIMUM 50 COUNT	STE0736535	13	Year(s)	Male Child	02-Jun-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS ND	PER0736549		Unknown	Female Adult	02-Jun-97	BLISTERS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WUN0737164	15	Year(s)	Female Child	05-Jun-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	JAV0737721		Unknown	Male Adult	10-Jun-97	ACNE	US	N	SKIN	2	006
CLEARASIL PADS MAXIMUM 50 COUNT	MC 0737767	13	Year(s)	Male Adult	10-Jun-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	REF0737727	13	Unknown	Female Adult	10-Jun-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	LEE0737625	16	Year(s)	Male Child	10-Jun-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	PAU0737974	18	Year(s)	Female Adult	11-Jun-97	BURNING	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	SAN0737814	17	Year(s)	Male Child	11-Jun-97	PEELING	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WUT0738324		Unknown	Female Adult	13-Jun-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	ALT0738525	13	Year(s)	Male Child	16-Jun-97	SWELLING	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LYN0738547		Unknown	Female Adult	16-Jun-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WES0738478	15	Unknown	Female Child	16-Jun-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	RIC0739093		Unknown	Male Child	19-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	TRA0739013	13	Year(s)	Female Child	19-Jun-97	STINGING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MAT0739301	16	Year(s)	Female Child	23-Jun-97	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	MOY0739739	17	Year(s)	Male Adult	24-Jun-97	ACNE	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WAD0739934	17	Year(s)	Female Child	25-Jun-97	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	PIE0740077		Unknown	Female Child	26-Jun-97	RASH	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KUL0740199		Unknown	Male Child	27-Jun-97	ACNE	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BES0740685		Unknown	Female Adult	01-Jul-97	BLISTERS	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JOH0740696		Unknown	Female Child	01-Jul-97	PIMPLES	US	N	SKIN	7	Day(s)
CLEARASIL PADS MAX NTNT 40 COUNT	HEI0740851	13	Year(s)	Female Child	02-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	MAR0741488	13	Year(s)	Male Adult	08-Jul-97	RASH	US	N	SKIN		Unknown
CLEARASIL PADS MAXIMUM 50 COUNT	HOU0741746		Unknown	Unknown	09-Jul-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	KEA0741796	28	Year(s)	Male Adult	09-Jul-97	SORES	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ROB0741767		Unknown	Female Child	09-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	DIL0742230	53	Year(s)	Female Adult	14-Jul-97	HEADACHE	US	N	SKIN	20	Minute(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BOW0742818	14	Year(s)	Male Child	17-Jul-97	RASH	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	WAD0742862	16	Year(s)	Male Child	17-Jul-97	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ZIN0743303	13	Year(s)	Female Child	21-Jul-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	LAC0743521		Unknown	Female Adult	22-Jul-97	PIMPLES	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	JET0743681	15	Year(s)	Female Child	23-Jul-97	BURNING	US	N	SKIN		
CLEARASIL PADS ND	LOP0744201		Unknown	Female Child	28-Jul-97	RASH	US	N	SKIN		
CLEARASIL PADS REG NTNT 40 COUNT	KAT0744715		Unknown	Male Adult	30-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BEC0745010	15	Year(s)	Female Child	01-Aug-97	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WHA0745334	12	Year(s)	Female Child	04-Aug-97	BUMPS	US	N	SKIN	1	Day(s)

DISC CLEARASIL PADS REGULAR STRENGTH ND	SAI0745190	18	Year(s)	Male Adult	04-Aug-97	REDNESS	US	N	SKIN	6	Day(s)
CLEARASIL PADS ND	GIL0745550	14	Year(s)	Female Adult	05-Aug-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WAL0746118	7	Year(s)	Female Child	08-Aug-97	REDNESS	US	N	SKIN	8	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	DAR0746295	16	Year(s)	Male Child	11-Aug-97	PEELING	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	UNK0746263		Unknown	Male Adult	11-Aug-97	PEELING	US	N	SKIN	2	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	JAM0746889	25	Year(s)	Male Adult	14-Aug-97	ACNE	US	N	SKIN	2	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LAS0747474	40	Year(s)	Female Adult	19-Aug-97	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	CAR0748542	14	Year(s)	Female Child	25-Aug-97	WELTS	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	PAL0749297	14	Year(s)	Female Child	29-Aug-97	PIMPLES	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	HOU0749794		Unknown	Male Adult	03-Sep-97	PEELING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	STR0750496	15	Year(s)	Female Child	08-Sep-97	SCRATCH	US	N	INJURY	3	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	ISA0751819		Unknown	Female Child	16-Sep-97	PEELING	US	N	SKIN	1	006
CLEARASIL PADS ND	SCA0753814	14	Year(s)	Female Child	26-Sep-97	BUMPS	US	N	SKIN		
CLEARASIL PADS ND	PRE0753995	15	Year(s)	Male Child	29-Sep-97	ACNE	US	N	SKIN	4	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	LED0754845	18	Year(s)	Female Adult	03-Oct-97	ACNE	US	N	SKIN	11	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	WRI0755606	13	Year(s)	Male Child	08-Oct-97	PIMPLES	US	N	SKIN	2	Week(s)
CLEARASIL PADS ND	SEU0756220	12	Year(s)	Female Child	10-Oct-97	RASH	US	N	SKIN		
CLEARASIL PADS ND	REC0756430	13	Year(s)	Female Child	13-Oct-97	IRRITATION	US	N	SKIN	4	Hour(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BER0757666		Unknown	Female Adult	20-Oct-97	SORES	US	N	SKIN	3	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	SHA0758902	12	Year(s)	Female Child	27-Oct-97	REDNESS	US	N	EYE	20	Hour(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	CAR0759462	13	Year(s)	Male Child	29-Oct-97	RASH	CA	N	SKIN	2	Week(s)
CLEARASIL PADS ND	ZAB0760896		Unknown	Male Adult	06-Nov-97	SORES	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	RUS0761178	13	Year(s)	Female Child	07-Nov-97	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	KEL0761465		Unknown	Male Adult	10-Nov-97	RASH	US	N	SKIN		
CLEARASIL PADS ND	REE0763110	14	Year(s)	Female Child	18-Nov-97	RASH	US	N	SKIN	5	Day(s)
CLEARASIL PADS MAXIMUM 50 COUNT	BOB0763556		Unknown	Unknown	20-Nov-97	REDNESS	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	KEN0773159	12	Year(s)	Male Child	21-Jan-98	RASH	US	N	SKIN		
CLEARASIL PADS ND	POG0773314		Unknown	Female Adult	22-Jan-98	ACNE	US	N	SKIN	3	Day(s)
CLR PADS REG 65 CT	RIC0773877	13	Year(s)	Female Child	26-Jan-98	REDNESS	CA	N	SKIN	12	Hour(s)
CLEARASIL PADS REG NTNT 40 COUNT	DIN0774705	15	Year(s)	Female Child	29-Jan-98	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	MUR0775061	15	Year(s)	Female Adult	30-Jan-98	STINGING	US	N	SKIN		
CLEARASIL PADS REG NTNT 40 COUNT	FEA0774951		Unknown	Unknown	30-Jan-98	STINGING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	EVA0775248	16	Year(s)	Female Child	02-Feb-98	RASH	US	N	SKIN		
CLEARASIL PADS MAX NTNT 40 COUNT	AVI0775588	14	Unknown	Female Adult	03-Feb-98	ACNE	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	FRA0775825		Unknown	Female Adult	04-Feb-98	REDNESS	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	AL-0777041		Unknown	Female Adult	11-Feb-98	BUMPS	US	N	SKIN		
CLEARASIL PADS ND	QUI0777120		Unknown	Female Child	11-Feb-98	BURNING	US	N	SKIN		

CLEARASIL PADS MAXIMUM 50 COUNT	ELK0779011	17	Year(s)	Female Child	24-Feb-98	RASH	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	MED0779619		Unknown	Unknown	26-Feb-98	BURNING	US	N	SKIN	3	Day(s)
CLEARASIL PADS ND	KAM0781053		Unknown	Unknown	06-Mar-98	BUMPS	US	N	SKIN	2	Week(s)
CLEARASIL PADS MAXIMUM 50 COUNT	ROM0782148	16	Year(s)	Male Child	12-Mar-98	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	VAR0782421		Unknown	Female Adult	13-Mar-98	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	FRY0783129		Unknown	Unknown	17-Mar-98	ACNE	US	N	SKIN	4	Day(s)
CLEARASIL PADS ND	WIL0787193	14	Year(s)	Male Adult	08-Apr-98	DRYNESS	US	N	SKIN	1	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	PAL0787524	12	Year(s)	Female Child	09-Apr-98	STINGING	US	N	SKIN		
CLEARASIL PADS ND	FIE0788176	14	Year(s)	Male Child	14-Apr-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	SAC0789133	15	Year(s)	Female Child	20-Apr-98	FLUSHED	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	SMI0790208		Unknown	Unknown	24-Apr-98	BUMPS	US	N	SKIN	5	Minute(s)
CLEARASIL PADS ND	CAS0794321	15	Year(s)	Male Child	19-May-98	PEELING	US	N	SKIN		
CLEARASIL PADS MAXIMUM 50 COUNT	LEE0796568	14	Year(s)	Female Child	03-Jun-98	RASH	US	N	SKIN	10	Minute(s)
CLR PADS REG 65 CT	X0798235	0	Unknown	Unknown	15-Jun-98	NONE	CA	N	SKIN		
CLEARASIL PADS ND	FLA0801495		Unknown	Female Adult	06-Jul-98	SCRATCH	US	N	SKIN		
CLEARASIL PADS ND	EDW0804435	19	Year(s)	Male Adult	20-Jul-98	SWELLING	US	N	SKIN	40	Minute(s)
CLEARASIL PADS ND	ANG0805062	21	Year(s)	Female Adult	22-Jul-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	JON0808076	13	Year(s)	Male Child	06-Aug-98	BURNING	US	N	SKIN		
CLEARASIL PADS ND	JON0808076	38	Year(s)	Female Adult	06-Aug-98	BURNING	US	N	SKIN	3	Week(s)
CLR PADS REG 65 CT	KOS0807830	16	Year(s)	Male Child	06-Aug-98	PIMPLES	CA	N	SKIN	1	006
CLEARASIL PADS ND	CUR0809365	14	Year(s)	Female Child	13-Aug-98	PIMPLES	CA	N	SKIN	3	Day(s)
CLR PADS REG 65 CT	KRU0809611	15	Year(s)	Male Child	14-Aug-98	ITCHING	CA	N	SKIN		
CLEARASIL PADS ND	BOB0810486		Unknown	Female Adult	20-Aug-98	DRYNESS	US	N	SKIN		Hour(s)
CLEARASIL PADS ND	REF0812055		Unknown	Female Child	28-Aug-98	DRYNESS	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	ZAR0812073		Unknown	Female Child	28-Aug-98	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	BOR0812248	11	Year(s)	Female Child	31-Aug-98	REDNESS	US	N	SKIN	7	Hour(s)
CLR PADS REG 65 CT	GIF0812494	19	Year(s)	Male Adult	01-Sep-98	REDNESS	CA	N	SKIN	1	Week(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	MON0812390	16	Year(s)	Female Child	01-Sep-98	RASH	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	CAN0813066	13	Year(s)	Male Child	03-Sep-98	ACNE	US	N	SKIN	2	Week(s)
CLEARASIL PADS REG NTNT 40 COUNT	SAN0816101	14	Year(s)	Male Child	24-Sep-98	REDNESS	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	CAR0822440	14	Year(s)	Male Child	04-Nov-98	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	FUL0827932	14	Year(s)	Female Child	08-Dec-98	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS ND	IRE0828843	2	Year(s)	Female Child	14-Dec-98	NONE	US	N	N		
CLEARASIL PADS ND	WIE0829058	13	Year(s)	Male Child	15-Dec-98	IRRITATION	US	N	EYE	2	Day(s)
CLEARASIL PADS ND	SOT0829666	20	Year(s)	Female Adult	18-Dec-98	REDNESS	US	N	SKIN	24	Hour(s)
CLEARASIL PADS ND	STA0831761		Unknown	Unknown	05-Jan-99	ACNE	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	REF0832174	20	Year(s)	Male Adult	07-Jan-99	SWELLING	US	N	SKIN	10	Minute(s)

CLEARASIL PADS ND	HEA0835056	16	Year(s)	Female Adult	25-Jan-99	REDNESS	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	DEL0836809	38	Year(s)	Female Adult	03-Feb-99	BURNING	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	LOP0836652	13	Year(s)	Male Adult	03-Feb-99	STINGING	US	N	SKIN	2	Day(s)
CLEARASIL PADS ND	THO0838996	13	Year(s)	Female Child	17-Feb-99	BURNING	US	N	SKIN		
CLEARASIL PADS ND	MOR0839859	13	Year(s)	Female Child	22-Feb-99	STINGING	US	N	SKIN	30	Minute(s)
CLEARASIL PADS ND	SIM0839868	17	Year(s)	Male Adult	22-Feb-99	PIMPLES	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	CAS0844117	15	Year(s)	Male Child	15-Mar-99	RASH	US	N	SKIN	3	Day(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	GRI0855323	39	Year(s)	Male Adult	17-May-99	SWELLING	US	N	SKIN	9	Hour(s)
CLEARASIL PADS ND	DIX0858976	13	Year(s)	Male Child	07-Jun-99	PEELING	US	N	SKIN		Unknown
CLR PADS REG 65 CT	CHI0861753	23	Year(s)	Male Adult	23-Jun-99	SCRATCH	CA	N	SKIN	1	Day(s)
CLR PADS REG 65 CT	HAI0865306	18	Year(s)	Female Adult	16-Jul-99	CUT, SCRATCH	CA	N	SKIN	3	Day(s)
CLEARASIL PADS ND	REF0867741	15	Year(s)	Female Adult	02-Aug-99	REDNESS	US	N	SKIN	12	Hour(s)
CLEARASIL PADS ND	LAR0870286		Unknown	Unknown	19-Aug-99	ACNE	US	N	SKIN		
CLEARASIL PADS ND	ALL0872950	17	Year(s)	Male Adult	07-Sep-99	PIMPLES	US	N	SKIN	1	Week(s)
DISC CLEARASIL PADS REGULAR STRENGTH ND	KRA0873972	17	Year(s)	Female Adult	13-Sep-99	ACNE	US	N	SKIN	3	Week(s)
CLEARASIL PADS ND	WIL0874791		Unknown	Male Adult	18-Sep-99	REDNESS	US	N	SKIN		
CLR PADS REG 65 CT	HOW0874918	14	Year(s)	Male Child	20-Sep-99	NONE	CA	N	N		
CLR PADS REG 65 CT	LEB0878042	14	Year(s)	Female Child	08-Oct-99	ITCHING	CA	N	SKIN	2	Day(s)
CLEARASIL PADS ND	JAC0878274	24	Year(s)	Unknown	11-Oct-99	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	BON0879569	1	Year(s)	Male Child	19-Oct-99	NONE	US	N	N		
CLEARASIL PADS ND	HOU0882550	18	Year(s)	Male Adult	08-Nov-99	RASH	CA	N	SKIN		
CLEARASIL PADS ND	KIN0884532	18	Year(s)	Female Adult	22-Nov-99	NONE	US	N	N		
CLR PADS REG 65 CT	KER0884445	10	Year(s)	Female Child	22-Nov-99	REDNESS	CA	N	SKIN		
CLEARASIL PADS ND	LUF0885868		Unknown	Unknown	02-Dec-99	REDNESS	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	MAR0889410	16	Year(s)	Female Child	30-Dec-99	RASH	US	N	SKIN	3	006
CLR PADS REG 65 CT	GAL0890565	15	Year(s)	Female Child	10-Jan-00	REDNESS	CA	N	SKIN	1	Week(s)
CLEARASIL PADS ND	HAU0897726		Unknown	Female Adult	26-Feb-00	IRRITATION	US	N	SKIN		
CLEARASIL PADS ND	JOH0900113	20	Year(s)	Female Adult	13-Mar-00	PIMPLES	US	N	SKIN	1	Week(s)
CLEARASIL PADS ND	HOO0901038		Unknown	Unknown	20-Mar-00	BUMPS	US	N	SKIN	5	Day(s)
CLEARASIL PADS ND	AND0903662		Unknown	Unknown	06-Apr-00	BURNING	US	N	SKIN		
DISC CLEARASIL PADS REGULAR STRENGTH ND	PON0908393	40	Year(s)	Female Adult	12-May-00	RASH	US	N	SKIN	1	Day(s)
CLEARASIL PADS ND	MIL0915098	25	Year(s)	Male Adult	10-Jul-00	REDNESS	CA	N	SKIN		
CLEARASIL PADS ND	ELS0915471			Unknown	13-Jul-00	DRYNESS	US	N	SKIN	1	Week(s)
CLR PADS REG 65 CT	ZOT0915940	14	Year(s)	Male Child	18-Jul-00	REDNESS	CA	N	SKIN	1	Week(s)
CLEARASIL PADS ND	REF0917598			Unknown	31-Jul-00	BURNING	US	N	EYE		
CLEARASIL PADS ND	RYA0917374			Female Adult	31-Jul-00	SWELLING	US	N	SKIN		
CLEARASIL PADS ND	SAU0922538			Unknown	12-Sep-00	BURNING	US	N	SKIN		

NA HEF Comm... for Clearasil Pads
1997-2000

CLEARASIL PADS ND	FOX0923678			Unknown	20-Sep-00	SCRATCH	US	N	SKIN		
CLEARASIL PADS ND	MIL0927666	22	Year(s)	Female Adult	16-Oct-00	BURNING	US	N	SKIN		
CLEARASIL PADS ND	HEN0928814				23-Oct-00	PIMPLES	US	N	SKIN		
CLEARASIL PADS ND	EST0929087			Unknown	25-Oct-00	DRYNESS	US	N	SKIN		
CLEARASIL PADS ND	CHA0931094	30	Year(s)	Female Adult	06-Nov-00	BURNING	US	N	SKIN		
CLR PADS REG 65 CT	FLA0935191	31	Year(s)	Female Adult	05-Dec-00	SCRATCH	CA	N	SKIN		
CLEARASIL PADS ND	KHO0936092			Unknown	12-Dec-00	REDNESS	US	N	SKIN		

NTS FOR NOXEMA PRODUCTS CONTAINING SALICYLIC ACID

NA HEF Comments for NOXZE products containing salicylic acid
1997-2000

Product Name	Inquiry #	Age	Age Unit	Species	Contact Date	Symptoms	Ctry	MD	Incident	Dur	Amount
NOX ORI PAD REG PAD NTNT 50 CT	BER0715899		Unknown	Male Adult	02-Jan-97	DRYNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	ALM0716299		Unknown	Female Child	06-Jan-97	SCRATCH	US	N	INJURY	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	SAQ0716449		Unknown	Female Adult	06-Jan-97	ACNE	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	YAN0716674	23	Year(s)	Female Adult	07-Jan-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BOW0716678	13	Year(s)	Female Child	07-Jan-97	RASH	US	N	SKIN	2	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	EVA0716615	35	Year(s)	Female Adult	07-Jan-97	SWELLING/INFLAMED	US	Y	SKIN	16	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAS0716665		Unknown	Female Child	07-Jan-97	DRYNESS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	REE0716500		Unknown	Female Adult	07-Jan-97	CUT, SCRATCH	US	N	INJURY	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0716569	14	Year(s)	Female Child	07-Jan-97	ITCHING	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	COO0716814	14	Year(s)	Female Child	08-Jan-97	SWELLING/INFLAMED	US	N	SKIN	1	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	MED0716879	14	Year(s)	Male Child	08-Jan-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	FUN0717050		Unknown	Male Adult	09-Jan-97	REDNESS	US	N	SKIN	4	Month(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BLU0717166	14	Year(s)	Unknown	10-Jan-97	ACNE	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	FLO0717496		Unknown	Female Adult	13-Jan-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	BOR0717460		Unknown	Female Adult	13-Jan-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	GAR0717504	14	Year(s)	Male Adult	13-Jan-97	BUMPS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	WHA0717457	10	Year(s)	Female Child	13-Jan-97	PIMPLES	US	N	SKIN		Unknown
NOX ORI PAD MAX PAD NTNT 50 CT	CUC0717736	12	Year(s)	Female Child	14-Jan-97	DRYNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	FAT0717746	11	Year(s)	Female Child	14-Jan-97	STINGING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	CLA0717927	14	Year(s)	Female Child	15-Jan-97	ACNE	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	GIB0717798		Unknown	Female Adult	15-Jan-97	BURNING	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	PAT0718100	17	Year(s)	Female Adult	16-Jan-97	REDNESS	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	PUC0718142	11	Year(s)	Female Child	16-Jan-97	BURNING	US	N	INHALATION		
NOX ORI PAD REG PAD NTNT 50 CT	RAS0718290	54	Year(s)	Male Adult	17-Jan-97	STINGING	US	N	EYE	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	MON0718186		Unknown	Female Adult	17-Jan-97	BOILS	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 8 OZ	HOL0718449		Unknown	Female Adult	21-Jan-97	BLISTERS	US	N	SKIN	3	Hour(s)
NOX ASPTC ASTR REG 8 OZ	SIM0718634		Unknown	Female Adult	21-Jan-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	CAI0718796		Unknown	Female Child	22-Jan-97	RASH	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DRO0718868	13	Year(s)	Female Child	22-Jan-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	GRA0718842	13	Year(s)	Male Adult	22-Jan-97	PIMPLES	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MCK0718818	19	Year(s)	Female Child	22-Jan-97	BURNING	US	Y	SKIN	3	Day(s)
D-NOX PADS REG STR ND	ROT0718947	11	Year(s)	Female Child	23-Jan-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HID0719013	13	Year(s)	Female Child	23-Jan-97	REDNESS	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	RHO0719066	14	Unknown	Male Adult	23-Jan-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0719063		Unknown	Unknown	23-Jan-97	ACNE	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	BRE0719243	30	Year(s)	Unknown	24-Jan-97	ACNE	US	N	SKIN	1	Week(s)

NOX ORI PAD REG PAD NTNT 50 CT	HUD0719235	16	Year(s)	Male Child	24-Jan-97	SORENESS	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	LAM0719387	15	Year(s)	Female Child	27-Jan-97	STINGING	US	N	SKIN	7	Minute(s)
NOX ORI PAD MAX PAD NTNT 50 CT	STE0719316		Unknown	Male Adult	27-Jan-97	SWELLING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	BIC0719748		Unknown	Female Adult	28-Jan-97	ACNE	US	N	SKIN	10	Day(s)
NOX ASPTC ASTR REG 8 OZ	WAL0719963		Unknown	Female Child	29-Jan-97	NONE	US	N	EYE		
NOX ORI PAD REG PAD NTNT 75 CT	MC 0719921		Unknown	Female Child	29-Jan-97	BURNING	US	N	SKIN	1	Minute(s)
D-NOX PADS REG STR ND	WAS0720084	23	Year(s)	Female Adult	30-Jan-97	BURNING	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAR0720069		Unknown	Female Adult	30-Jan-97	RASH	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR REG 8 OZ	JEN0720339	15	Year(s)	Male Child	31-Jan-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	STR0720343	18	Year(s)	Male Adult	31-Jan-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BLA0720323	24	Year(s)	Female Adult	31-Jan-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	JON0720271		Unknown	Female Adult	31-Jan-97	REDNESS	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 50 CT	FRE0720434		Unknown	Female Adult	03-Feb-97	SCRATCH	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BOW0720858		Unknown	Female Child	04-Feb-97	BUMPS	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MC 0720742	15	Year(s)	Male Child	04-Feb-97	BUMPS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MC 0720742		Unknown	Female Adult	04-Feb-97	BUMPS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOR0720857	12	Year(s)	Female Child	04-Feb-97	WELTS	US	N	SKIN		
D-NOX PADS REG STR ND	MC 0721035	11	Year(s)	Male Child	05-Feb-97	HEADACHE	US	N	INHALATION		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	FIT0721042	8	Year(s)	Female Child	05-Feb-97	NONE	US	N	INGESTION		
NOX ORI PAD MAX PAD NTNT 50 CT	POR0720951	15	Year(s)	Male Child	05-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MAC0721178	17	Year(s)	Female Child	06-Feb-97	REDNESS	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 4 OZ	SHE0721196	10	Year(s)	Female Child	07-Feb-97	NONE	US	N	INGESTION		
NOX ORI PAD MAX PAD NTNT 50 CT	COV0721206	17	Year(s)	Male Child	07-Feb-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	JOH0721317		Unknown	Female Child	07-Feb-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOO0721381	17	Year(s)	Female Child	07-Feb-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	PAC0721620	13	Year(s)	Female Child	10-Feb-97	ACNE	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	ROB0721815	13	Year(s)	Female Child	11-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	BUT0721761		Unknown	Male Adult	11-Feb-97	SWELLING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	JOH0721713	15	Year(s)	Female Child	11-Feb-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	KLI0721958		Unknown	Female Adult	12-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	FRE0721994		Unknown	Female Child	12-Feb-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	JAC0721867		Unknown	Female Adult	12-Feb-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	SAN0722152	16	Year(s)	Female Child	13-Feb-97	STINGING	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	HAY0722293		Unknown	Female Adult	14-Feb-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH TOTAL	WOM0722388	16	Year(s)	Male Child	14-Feb-97	ACNE	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	CRA0722408		Unknown	Female Adult	18-Feb-97	BURNING	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	FRE0722464	13	Year(s)	Female Child	18-Feb-97	DRYNESS	US	N	SKIN	2	Week(s)

NOX ASPTC ASTR REG 8 OZ	BAL0722831	17	Year(s)	Female Child	19-Feb-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	MAR0722798		Unknown	Female Adult	19-Feb-97	RASH	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HAG0722826		Unknown	Female Adult	19-Feb-97	ACNE	US	N	SKIN		
D-NOX PADS REG STR ND	TRE0722915	14	Year(s)	Male Child	20-Feb-97	ACNE	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	BAU0723053	15	Year(s)	Male Child	20-Feb-97	PIMPLES	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LOP0722974	18	Year(s)	Male Adult	20-Feb-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	PAR0723358	16	Year(s)	Female Adult	24-Feb-97	BUMPS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	KAM0723587	19	Year(s)	Female Adult	25-Feb-97	ACNE	US	N	SKIN	1	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	REE0723502		Unknown	Female Adult	25-Feb-97	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	TRU0723745		Unknown	Unknown	26-Feb-97	STINGING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	RIV0723825	11	Year(s)	Female Child	26-Feb-97	REDNESS	US	N	SKIN	30	Year(s)
NOX ORI PAD REG PAD NTNT 50 CT	MIL0723815		Unknown	Male Adult	26-Feb-97	ACNE	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	SIP0723905	14	Year(s)	Female Child	27-Feb-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	LAM0724291		Unknown	Female Adult	03-Mar-97	ITCHING	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MEE0724315	15	Year(s)	Male Adult	03-Mar-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BUR0724576	12	Year(s)	Female Child	04-Mar-97	ACNE	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	ROB0724611	18	Year(s)	Female Adult	05-Mar-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	BRO0724937	10	Year(s)	Male Child	06-Mar-97	BUMPS	US	N	SKIN	3	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HOL0724956	17	Year(s)	Female Child	06-Mar-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	JET0725062	13	Unknown	Female Child	07-Mar-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	PAC0724992		Unknown	Female Adult	07-Mar-97	RASH	US	N	SKIN	7	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JOH0725394	18	Year(s)	Female Child	10-Mar-97	BUMPS	US	N	SKIN	5	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	PAD0725411	13	Year(s)	Male Child	11-Mar-97	PIMPLES	US	N	SKIN	3	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	JOH0725757	15	Year(s)	Female Child	12-Mar-97	PIMPLES	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	LAR0725922	14	Year(s)	Female Child	13-Mar-97	HIVES	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DAV0726046		Unknown	Female Adult	14-Mar-97	SORES	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	WOJ0726082	12	Year(s)	Female Child	14-Mar-97	RASH	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	WIL0725966		Unknown	Female Adult	14-Mar-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	VAN0726360	15	Year(s)	Female Child	17-Mar-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	CAR0726701		Unknown	Female Adult	19-Mar-97	SORENESS	US	N	SKIN	12	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAR0726763	15	Year(s)	Female Adult	19-Mar-97	PIMPLES	US	N	SKIN	3	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	REF0727004		Unknown	Female Child	20-Mar-97	ACNE	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	TER0727244	34	Year(s)	Female Adult	24-Mar-97	RASH	US	N	SKIN	5	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SMI0727412	11	Year(s)	Female Child	24-Mar-97	REDNESS	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	TOM0727653	12	Year(s)	Female Child	25-Mar-97	RASH	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	VER0727602	13	Year(s)	Male Child	25-Mar-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	VAL0727585		Unknown	Female Child	25-Mar-97	BUMPS	US	N	SKIN	2	Day(s)

NOX ORI PAD MAX PAD NTNT 50 CT	WIL0727703		Unknown	Female Adult	26-Mar-97	TEARING	US	N	EYE INDIRECT		
D-NOX PADS REG STR ND	AGA0727861	43	Year(s)	Female Adult	27-Mar-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	TAS0727947	12	Year(s)	Female Child	27-Mar-97	PIMPLES	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HER0727930		Unknown	Female Child	27-Mar-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	FRI0728030	52	Year(s)	Female Adult	31-Mar-97	RASH	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	FAR0728263	14	Year(s)	Female Child	31-Mar-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	AUE0728297	30	Year(s)	Female Adult	01-Apr-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	GUE0728293	23	Year(s)	Female Adult	01-Apr-97	PIMPLES	US	N	SKIN	6	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	BEC0728642	13	Year(s)	Female Child	02-Apr-97	BUMPS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	NOR0728512	17	Year(s)	Female Adult	02-Apr-97	REDNESS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	WAT0728692	12	Year(s)	Female Adult	03-Apr-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	CHI0729195		Unknown	Male Child	07-Apr-97	PIMPLES	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	TUC0729095		Unknown	Male Adult	07-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HER0729619	12	Year(s)	Female Child	09-Apr-97	ACNE	US	N	SKIN		Unknown
NOX ORI PAD REG PAD NTNT 50 CT	MAR0729563		Unknown	Female Adult	09-Apr-97	REDNESS	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	PEO0729610	13	Year(s)	Female Child	09-Apr-97	RASH	US	N	SKIN	2	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MOO0729625	27	Year(s)	Male Adult	09-Apr-97	SORES	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	MIT0729666		Unknown	Female Adult	10-Apr-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	DOB0729731	14	Unknown	Female Adult	10-Apr-97	DIFFICULTY	US	N	INHALATION		
NOX ORI PAD REG PAD NTNT 50 CT	HAL0729875		Unknown	Female Adult	11-Apr-97	SCRATCH	US	N	INJURY		
NOX ORI PAD MAX PAD NTNT 50 CT	REI0730019		Unknown	Female Adult	14-Apr-97	DISCOLORATION	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	GAR0730421	13	Year(s)	Female Child	15-Apr-97	PEELING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	ARC0730437	28	Year(s)	Female Adult	15-Apr-97	NONE	US	N	ORAL/NASAL		
NOX ASPTC ASTR XTR 8 OZ	STI0730320	16	Year(s)	Female Child	15-Apr-97	REDNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MOR0730358	35	Year(s)	Female Adult	15-Apr-97	IRRITATION	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SAL0730521		Unknown	Female Adult	16-Apr-97	BURN	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	VAN0730782	5	Year(s)	Female Child	17-Apr-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	STE0730660	56	Year(s)	Female Adult	17-Apr-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	HOE0730980		Unknown	Female Adult	18-Apr-97	DRYNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	DON0730842	13	Year(s)	Female Child	18-Apr-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HEC0730937	11	Year(s)	Female Child	18-Apr-97	NAUSEA	US	N	INHALATION		
NOX ORI PAD REG PAD NTNT 50 CT	SCH0731081	18	Year(s)	Male Adult	21-Apr-97	RASH	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	ELL0731492	13	Year(s)	Female Child	22-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ROS0731358		Unknown	Male Adult	22-Apr-97	BURN	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	REF0731572		Unknown	Unknown	23-Apr-97	PIMPLES	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	EHR0731789		Unknown	Female Adult	24-Apr-97	FLAKING	US	N	SKIN	3	Day(s)
D-NOX PADS REG STR ND	RED0732122	11	Year(s)	Male Child	28-Apr-97	IRRITATION	US	N	SKIN	2	Month(s)

NOX ORI PAD MAX PAD NTNT 50 CT	WIL0732230	15	Year(s)	Male Child	28-Apr-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	ROS0732148	16	Year(s)	Male Child	28-Apr-97	ACNE	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	JON0732212	18	Year(s)	Female Adult	28-Apr-97	HAIR LOSS (DIFFUSE)	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	ARA0732382	17	Year(s)	Male Child	29-Apr-97	DRYNESS	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	KOU0732532	16	Year(s)	Female Adult	30-Apr-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ROB0732590		Unknown	Female Adult	30-Apr-97	PIMPLES	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	JAC0732520	14	Year(s)	Male Adult	30-Apr-97	BLEMISHES	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	AMO0732683		Unknown	Unknown	01-May-97	DIFFICULTY	US	N	INHALATION	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	LOP0732629	18	Year(s)	Female Child	01-May-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	BAY0733370	13	Year(s)	Female Child	06-May-97	PIMPLES	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LEV0733503	17	Year(s)	Female Child	07-May-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	GON0733598	14	Year(s)	Male Child	12-May-97	DISCOLORATION	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	LOU0733630	15	Year(s)	Female Adult	12-May-97	BURNING	US	N	SKIN		Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	KUM0733942		Unknown	Female Child	12-May-97	STINGING	US	N	SKIN	5	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	MOO0733838	11	Year(s)	Female Child	12-May-97	ACNE	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CRA0733962	22	Year(s)	Female Adult	12-May-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	CAS0733981	16	Year(s)	Male Adult	13-May-97	ACNE	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JUN0734040	13	Unknown	Unknown	13-May-97	PIMPLES	US	N	SKIN	4	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	LIN0734060		Unknown	Female Adult	13-May-97	STINGING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	HAS0734315	12	Year(s)	Male Child	14-May-97	ACNE	US	N	SKIN	3	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	ROM0734309	30	Year(s)	Female Adult	14-May-97	ACNE	US	N	SKIN	3	Day(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	BRO0734594	3	Year(s)	Female Child	16-May-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR REG 8 OZ	BRA0734606	16	006	Female Child	16-May-97	NONE	US	N	EYE		
NOX ORI PAD MAX PAD NTNT 50 CT	TRA0734522	13	Year(s)	Female Child	16-May-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	DUN0734651		Unknown	Female Adult	19-May-97	SORES	US	Y	SKIN	5	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	SAL0734697		Unknown	Female Child	19-May-97	REDNESS	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	VUC0735038	15	Year(s)	Female Child	20-May-97	RASH	US	N	SKIN	2	Day(s)
D-NOX PADS REG STR ND	FAC0735303		Unknown	Female Adult	21-May-97	CUT, SCRATCH	US	N	INJURY	8	Hour(s)
D-NOX PADS REG STR ND	ROB0735241		Unknown	Female Adult	21-May-97	BURN	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ARM0735268	13	Year(s)	Female Child	21-May-97	RASH	US	N	SKIN	12	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	KEN0735273	19	Unknown	Female Adult	21-May-97	RASH	US	N	SKIN	3	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	PEN0735496	2	Year(s)	Female Child	22-May-97	NONE	US	N	INGESTION		
D-NOX PADS REG STR ND	WIL0735612	17	Year(s)	Female Adult	23-May-97	ACNE	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	CEC0735619		Unknown	Male Adult	23-May-97	ACNE	US	N	SKIN		Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	HER0735618	16	Year(s)	Unknown	23-May-97	PIMPLES	US	N	SKIN	3	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LEV0735544		Unknown	Female Adult	23-May-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	TOY0735601		Unknown	Female Adult	23-May-97	SCRATCH	US	N	INJURY	3	Day(s)

D-NOX PADS REG STR ND	WEI0735779		Unknown	Male Adult	27-May-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	WIL0735836		Unknown	Female Adult	27-May-97	DRYNESS	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	GOR0735657	47	Year(s)	Female Adult	27-May-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	MOB0735899		Unknown	Female Adult	28-May-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	BAC0736241		Unknown	Female Child	29-May-97	BLEMISHES	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MAR0736259	34	Year(s)	Female Adult	29-May-97	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	WES0736156		Unknown	Male Adult	29-May-97	SCRATCH	US	N	INJURY	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	COL0736257	42	Year(s)	Female Adult	29-May-97	(GENERALIZED)	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	BRO0736278		Unknown	Female Adult	30-May-97	RASH	US	N	SKIN	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	RUS0736481		Unknown	Female Adult	02-Jun-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	JOH0736636	15	Year(s)	Female Child	02-Jun-97	ACNE	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	LOC0736546	12	Year(s)	Female Child	02-Jun-97	ACNE	US	N	SKIN	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	CAM0736788	18	Year(s)	Female Adult	03-Jun-97	REDNESS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	DUL0736856		Unknown	Female Adult	03-Jun-97	PIMPLES	US	N	SKIN	3	Day(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	MIL0736977	3	Year(s)	Male Child	04-Jun-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	KES0736899		Unknown	Female Adult	04-Jun-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	KLE0736951	75	Year(s)	Female Adult	04-Jun-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	CHA0737042	17	Year(s)	Male Child	04-Jun-97	PIMPLES	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MAR0737188	12	Year(s)	Female Child	05-Jun-97	TEARING	US	N	EYE INDIRECT		
NOX ORI PAD REG PAD NTNT 50 CT	GUN0737176	17	Year(s)	Female Adult	05-Jun-97	REDNESS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LUN0737130		Unknown	Female Adult	05-Jun-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	HEW0737280		Unknown	Female Adult	06-Jun-97	PIMPLES	US	N	SKIN	6	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SMI0737330	14	Year(s)	Female Child	06-Jun-97	RASH	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MC 0737287	15	Year(s)	Female Child	06-Jun-97	REDNESS	US	N	SKIN	3	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	BAI0737565		Unknown	Male Child	09-Jun-97	PIMPLES	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	ROO0737703	18	006	Male Child	10-Jun-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR REG 8 OZ	SAU0737775	42	Unknown	Female Adult	10-Jun-97	BURNING	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	LLE0737663	14	Year(s)	Female Child	10-Jun-97	ACNE	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	ALL0737589	17	Year(s)	Male Adult	10-Jun-97	ACNE	US	N	SKIN	4	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	NEI0737882	16	Year(s)	Female Child	11-Jun-97	RASH	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	JAM0738159	9	Year(s)	Male Child	12-Jun-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	MC 0738075		Unknown	Unknown	12-Jun-97	PIMPLES	US	N	SKIN	10	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	DEL0738051		Unknown	Female Adult	12-Jun-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	BER0738297	18	Unknown	Male Adult	13-Jun-97	BURNING	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	DYC0738563	16	Year(s)	Female Adult	16-Jun-97	PIMPLES	US	N	SKIN	3	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DEN0738730	12	Year(s)	Female Child	17-Jun-97	BUMPS	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MAL0738739	15	Year(s)	Female Child	17-Jun-97	BUMPS	US	N	SKIN	2	Week(s)

NOX ORI PAD MAX PAD NTNT 50 CT	MC 0738965	11	Year(s)	Female Child	19-Jun-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	TOL0739262	15	Year(s)	Female Child	20-Jun-97	BURN	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	MUR0739460	11	Year(s)	Female Child	23-Jun-97	BUMPS	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	BAR0739466		Unknown	Female Adult	23-Jun-97	BURNING	US	N	SKIN		Minute(s)
NOX ORI PAD MAX PAD NTNT 50 CT	CHA0739326	17	Year(s)	Female Child	23-Jun-97	REDNESS	US	N	SKIN	4	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	FIS0739353	38	Year(s)	Female Adult	23-Jun-97	SCRATCH	US	N	INJURY		
NOXZEMA PADS MAXIMUM STRENGTH ND	LIS0739372		Unknown	Female Child	23-Jun-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	PHI0739364	14	Year(s)	Female Child	23-Jun-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	LEW0739904	16	Year(s)	Male Child	25-Jun-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	TAY0739858	13	Year(s)	Female Child	25-Jun-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 50 CT	ZIP0739817		Unknown	Female Child	25-Jun-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	HAL0739903		Unknown	Female Adult	25-Jun-97	REDNESS	US	N	SKIN	24	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MOR0740275	15	Year(s)	Female Child	27-Jun-97	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	HAL0740538		Unknown	Female Adult	30-Jun-97	PIMPLES	US	N	SKIN	10	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MAR0740688	24	Year(s)	Unknown	01-Jul-97	BURNING	US	N	SKIN	6	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	STE0740694		Unknown	Unknown	01-Jul-97	IRRITATION	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	MIL0740868	15	Year(s)	Female Adult	02-Jul-97	ACNE	US	N	SKIN	3	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MUE0740925	20	Year(s)	Female Adult	02-Jul-97	BLISTERS	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SAZ0740790	16	Year(s)	Female Child	02-Jul-97	DRYNESS	US	N	SKIN		Day(s)
NOX ACNE PADS REG 90 CT	OWE0741125		Unknown	Female Adult	07-Jul-97	STINGING	US	N	SKIN	6	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	ROE0741569	13	Year(s)	Female Child	08-Jul-97	BURNING	US	N	EYE INDIRECT		
NOX ORI PAD REG PAD NTNT 75 CT	KAY0741575	13	Year(s)	Female Child	08-Jul-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOY0741526		Unknown	Female Adult	08-Jul-97	ACNE	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SCH0741941	10	006	Male Child	10-Jul-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	NEA0741832	21	Year(s)	Female Adult	10-Jul-97	BURNING	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	BUR0742074	11	Year(s)	Female Child	11-Jul-97	BURNING	US	N	EYE INDIRECT		
NOXZEMA PADS MAXIMUM STRENGTH ND	STA0742053	14	Year(s)	Female Child	11-Jul-97	STINGING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	O^B0742457	26	Year(s)	Female Adult	15-Jul-97	ACNE	US	N	SKIN	6	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	O C0742614		Unknown	Female Adult	16-Jul-97	PEELING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	BAN0742647	13	Year(s)	Unknown	16-Jul-97	PIMPLES	US	N	SKIN	2	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	WEB0742738		Unknown	Female Adult	16-Jul-97	SWELLING	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HAM0742802		Unknown	Female Adult	17-Jul-97	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	TOL0742909	13	Year(s)	Female Child	17-Jul-97	BUMPS	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	HAY0743293		Unknown	Female Child	21-Jul-97	RASH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	BLA0743434		Unknown	Female Adult	22-Jul-97	CUT	US	N	INJURY	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	GAL0743495	28	Year(s)	Female Adult	22-Jul-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	PHI0743416		Unknown	Male Adult	22-Jul-97	REDNESS	US	N	SKIN		

NOX ASPTC ASTR XTR 8 OZ	JEA0743664		Unknown	Unknown	23-Jul-97	PEELING	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR REG 8 OZ	REF0743847		Unknown	Unknown	24-Jul-97	STINGING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	WUN0743783	16	Year(s)	Female Child	24-Jul-97	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	WUN0743783	18	Year(s)	Male Adult	24-Jul-97	RASH	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	JOH0743808		Unknown	Unknown	24-Jul-97	REDNESS	US	N	SKIN	3	Hour(s)
NOX ORI PAD REG PAD NTNT 50 CT	MIN0743744	15	Year(s)	Male Child	24-Jul-97	SCRATCH	US	N	SKIN	14	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DON0743957	13	Year(s)	Female Child	25-Jul-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BOR0744052	13	Year(s)	Female Child	25-Jul-97	RASH	US	N	SKIN	2	Week(s)
NOX ACNE PADS REG 65 CT	TUR0744311		Unknown	Female Adult	28-Jul-97	REDNESS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SNO0744242		Unknown	Female Adult	28-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	TAY0744427	13	Year(s)	Female Child	29-Jul-97	ACNE	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	AJI0744526		Unknown	Female Adult	29-Jul-97	BURNING	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	MUR0744507		Unknown	Male Child	29-Jul-97	BUMPS	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	MER0744627		Unknown	Unknown	30-Jul-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	KAS0744700		Unknown	Unknown	30-Jul-97	DISCOLORATION	US	N	SKIN	6	Day(s)
NOX ASPTC ASTR XTR 8 OZ	DEC0744883		Unknown	Female Adult	31-Jul-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	ROE0744788	10	Year(s)	Female Child	31-Jul-97	STINGING	US	N	EYE INDIRECT		
NOXZEMA PADS MAXIMUM STRENGTH ND	NAP0744954	33	Year(s)	Female Adult	01-Aug-97	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	ING0745310	18	Year(s)	Female Child	04-Aug-97	ACNE	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	SOL0745271	13	Year(s)	Female Child	04-Aug-97	ACNE	US	N	SKIN	3	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	DIG0745205		Unknown	Female Child	04-Aug-97	TEARING	US	N	EYE INDIRECT		
NOX ACNE PADS REG 90 CT	MAL0745525	15	Year(s)	Female Adult	05-Aug-97	SNEEZING	US	N	INHALATION		
NOX ASPTC ASTR XTR 8 OZ	MIL0745598		Unknown	Male Adult	05-Aug-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	WAL0745389		Unknown	Female Adult	05-Aug-97	REDNESS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	MON0745603	12	Year(s)	Female Adult	05-Aug-97	PIMPLES	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	HOR0745885		Unknown	Unknown	07-Aug-97	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	ANS0745854	18	Year(s)	Male Adult	07-Aug-97	REDNESS	US	N	SKIN	2	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	ENG0745847	15	Year(s)	Female Child	07-Aug-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	HOW0745891	13	Year(s)	Female Child	07-Aug-97	ACNE	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	ALV0745996	12	Year(s)	Female Adult	08-Aug-97	STINGING	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	FIS0746023		Unknown	Unknown	08-Aug-97	FLAKING	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	KRA0745976		Unknown	Female Adult	08-Aug-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	MAI0746029	15	Year(s)	Female Adult	08-Aug-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	LEO0745981	29	Year(s)	Female Adult	08-Aug-97	NUMBNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	DOO0746303	12	Year(s)	Female Child	11-Aug-97	PIMPLES	US	N	SKIN	30	Year(s)
NOX ORI PAD REG PAD NTNT 50 CT	KRA0746281	44	Year(s)	Female Adult	11-Aug-97	TEARING	US	N	EYE INDIRECT		
NOX ACNE PADS MAX 65 CT	FIS0746556	13	Year(s)	Female Child	12-Aug-97	REDNESS	US	N	SKIN	1	Week(s)

NOX ACNE PADS MAX 65 CT	WOO0746582		Unknown	Female Adult	12-Aug-97	RASH	US	N	SKIN	4	Day(s)
NOX ACNE PADS MAX 90 CT	MON0746578		Unknown	Female Adult	12-Aug-97	BURNING	US	Y	SKIN		Unknown
NOX ACNE PADS MAX 90 CT	MOF0746605		Unknown	Female Adult	13-Aug-97	PEELING	US	N	SKIN	1	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	SQU0746768	13	Year(s)	Female Child	13-Aug-97	PEELING	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	ALQ0746734		Unknown	Female Child	13-Aug-97	IRRITATION	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 65 CT	AUL0746986	15	Year(s)	Female Adult	14-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	BYF0747343	14	Year(s)	Male Child	18-Aug-97	REDNESS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	BYF0747343		Unknown	Female Adult	18-Aug-97	REDNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	FUN0747273		Unknown	Male Adult	18-Aug-97	SCARS	US	Y	SKIN	6	Month(s)
NOX ACNE PADS MAX 65 CT	ELD0747478		Unknown	Female Adult	19-Aug-97	BURNING	US	N	SKIN	3	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JOH0747623		Unknown	Female Child	19-Aug-97	PIMPLES	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 65 CT	MC 0747838		Unknown	Female Adult	20-Aug-97	DRYNESS	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 4 OZ	THO0747881		Unknown	Female Child	20-Aug-97	REDNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	JAC0747785		Unknown	Unknown	20-Aug-97	REDNESS	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	STO0748039	13	Year(s)	Female Child	21-Aug-97	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	RHO0747978		Unknown	Unknown	21-Aug-97	REDNESS	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	ELL0748224		Unknown	Female Adult	22-Aug-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	ELW0748107		Unknown	Female Adult	22-Aug-97	RASH	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 90 CT	FOL0748145	11	Year(s)	Unknown	22-Aug-97	DRYNESS	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	HAR0748184	14	Year(s)	Female Child	22-Aug-97	PIMPLES	US	N	SKIN		Day(s)
NOX ASPTC ASTR REG 8 OZ	ROT0748710		Unknown	Female Adult	26-Aug-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	DEZ0749336	14	Year(s)	Female Child	29-Aug-97	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	NIP0749647		Unknown	Unknown	02-Sep-97	BURNING	US	N	SKIN	4	Hour(s)
NOX ACNE PADS REG 65 CT	WIL0749450	21	Year(s)	Female Adult	02-Sep-97	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	DIR0749460		Unknown	Female Adult	02-Sep-97	SWELLING	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MUR0749574		Unknown	Male Adult	02-Sep-97	STINGING	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	MON0749831	19	Year(s)	Female Adult	03-Sep-97	ACNE	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 8 OZ	WIL0749707		Unknown	Female Adult	03-Sep-97	BLISTERS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	ROS0750061	14	Year(s)	Female Child	04-Sep-97	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	THO0750052	18	Year(s)	Female Adult	04-Sep-97	SORES	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 8 OZ	WON0749946	46	Unknown	Male Adult	04-Sep-97	REDNESS	CA	N	SKIN	3	Week(s)
NOX ASPTC ASTR REG 8 OZ	WES0750478	4	Year(s)	Male Child	08-Sep-97	DROWSINESS	US	N	INGESTION	20	Minute(s)
NOX ACNE PADS REG 65 CT	BUT0751209	11	Year(s)	Female Child	11-Sep-97	PIMPLES	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	ROB0751380		Unknown	Female Adult	12-Sep-97	CRACKING	US	N	SKIN	1	Month(s)
NOX ACNE PADS MAX 90 CT	SAN0752171	17	Year(s)	Male Adult	17-Sep-97	PIMPLES	US	N	SKIN	1	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	BLA0752577		Unknown	Unknown	19-Sep-97	PIMPLES	US	N	SKIN		
NOX ACNE PADS REG 90 CT	HAC0752825		Unknown	Female Adult	22-Sep-97	SCRATCH	US	N	INJURY	2	Day(s)

NOX ACNE PADS REG 90 CT	MOR0752816		Unknown	Female Adult	22-Sep-97	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BRA0752962	13	Year(s)	Female Adult	22-Sep-97	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	HAL0752932	31	Year(s)	Female Adult	22-Sep-97	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	BRE0753125	12	Year(s)	Female Child	23-Sep-97	REDNESS	CA	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	DAV0753362	16	Year(s)	Male Child	24-Sep-97	SWELLING	US	N	SKIN	3	Minute(s)
NOX ORI PAD MAX PAD NTNT 50 CT	SIL0753605	13	Year(s)	Female Child	25-Sep-97	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	CIR0754120	14	Year(s)	Female Child	29-Sep-97	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	BAN0754072		Unknown	Female Adult	29-Sep-97	PEELING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	MIT0754291		Unknown	Male Adult	30-Sep-97	PEELING	US	N	SKIN		Day(s)
NOX ACNE PADS MAX 90 CT	LIG0754422		Unknown	Female Adult	01-Oct-97	PIMPLES	US	N	SKIN	4	Day(s)
NOX ACNE PADS REG 90 CT	CER0754563	12	Year(s)	Female Child	02-Oct-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	CES0754709	21	Year(s)	Male Adult	02-Oct-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	KAU0754953	28	Year(s)	Female Adult	03-Oct-97	TINGLING	US	N	INGESTION	5	Minute(s)
NOX ASPTC ASTR REG 8 OZ	GRE0755557	8	Year(s)	Male Child	07-Oct-97	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	BEA0755805	12	Year(s)	Female Child	08-Oct-97	ACNE	US	N	SKIN	1.5	Week(s)
D-NOX PADS REG STR ND	NEM0756189	16	Year(s)	Female Child	10-Oct-97	ACNE	CA	N	SKIN	6	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	FOR0756258		Unknown	Male Adult	10-Oct-97	BUMPS	US	N	SKIN	2	Month(s)
NOX ACNE PADS MAX 90 CT	COR0756747		Unknown	Female Adult	14-Oct-97	BURNING	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR REG 8 OZ	MAN0756750	14	Unknown	Female Child	14-Oct-97	DRYNESS	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	LUT0756841	13	Year(s)	Female Child	15-Oct-97	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HER0757214	22	Year(s)	Female Adult	16-Oct-97	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	NEA0757064	26	Year(s)	Female Adult	16-Oct-97	REDNESS	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	COM0757390		Unknown	Female Adult	17-Oct-97	REDNESS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	PET0757450	18	006	Male Child	17-Oct-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR REG 8 OZ	SMI0757321		Unknown	Unknown	17-Oct-97	REDNESS	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 65 CT	ALV0757766		Unknown	Female Adult	20-Oct-97	RASH	US	N	SKIN		
NOX ACNE PADS REG 90 CT	KIN0757868	17	Year(s)	Male Child	21-Oct-97	SWELLING	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	JOI0758163	3	Year(s)	Male Child	22-Oct-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	COL0758095	15	Year(s)	Female Adult	22-Oct-97	SWELLING	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	REF0758383		Unknown	Unknown	23-Oct-97	SWELLING	US	N	SKIN		
NOX ACNE PADS REG 90 CT	GRE0758390		Unknown	Male Adult	23-Oct-97	SWELLING	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	LAN0759263	19	006	Female Child	28-Oct-97	REDNESS	US	N	EYE		Unknown
NOX ACNE PADS REG 65 CT	BAR0759246		Unknown	Female Adult	28-Oct-97	SCRATCH	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	DAU0759086	13	Year(s)	Female Child	28-Oct-97	STINGING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	BUG0759048	13	Year(s)	Female Child	28-Oct-97	RASH	CA	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	LED0759349		000	Unknown	29-Oct-97	SHORT OF BREATH	CA	N	INHALATION		
NOXZEMA PADS MAXIMUM STRENGTH ND	SMI0759505	14	Year(s)	Female Child	29-Oct-97	REDNESS	US	N	SKIN	2	Day(s)

NOX ACNE PADS MAX 65 CT	LAW0759837		Unknown	Female Adult	31-Oct-97	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	HEL0760644	11	Year(s)	Female Child	05-Nov-97	TEARING	US	N	EYE INDIRECT		
NOX ORI PAD MAX PAD NTNT 50 CT	COM0760790	12	Year(s)	Female Child	05-Nov-97	ACNE	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ADA0760817		Unknown	Unknown	06-Nov-97	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	JAC0761028	31	Year(s)	Female Adult	07-Nov-97	ITCHING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	STU0761228		Unknown	Female Adult	07-Nov-97	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	ADA0761151	13	Year(s)	Female Child	07-Nov-97	ACNE	US	N	SKIN	8	Day(s)
NOX ACNE PADS MAX 65 CT	WEB0761373	30	Year(s)	Female Adult	10-Nov-97	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	CEL0761647	13	Year(s)	Female Child	11-Nov-97	REDNESS	US	N	EYE INDIRECT		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	BOD0762263	12	Year(s)	Female Child	13-Nov-97	RASH	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	SAN0762124		Unknown	Female Adult	13-Nov-97	RASH	US	N	SKIN	2	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	HIG0762342		Unknown	Female Adult	14-Nov-97	SWELLING	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	ENR0762665	16	Year(s)	Female Adult	17-Nov-97	PIMPLES	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	RIT0762560	11	Year(s)	Male Child	17-Nov-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	KHA0762847	22	Year(s)	Female Adult	17-Nov-97	REDNESS	CA	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	LUT0763029		Unknown	Female Adult	18-Nov-97	REDNESS	US	N	SKIN	4	Day(s)
NOX ACNE PADS MAX 65 CT	HO0763347	23	Year(s)	Female Adult	19-Nov-97	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SUL0763404	14	Year(s)	Male Child	19-Nov-97	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	WET0763314		Unknown	Female Adult	19-Nov-97	WELTS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	SNY0763180	30	Year(s)	Female Adult	19-Nov-97	SCRATCH	US	N	INJURY	1	Day(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	HEL0763673		Unknown	Female Adult	21-Nov-97	DRYNESS	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	KID0763864	12	Year(s)	Female Child	21-Nov-97	ACNE	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	GOM0763895	2	Year(s)	Male Child	21-Nov-97	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 75 CT	FIN0763894	18	Year(s)	Female Adult	21-Nov-97	BURNING	US	N	EYE INDIRECT		
D-NOX PADS REG STR ND	CUN0764184	17	Year(s)	Female Child	24-Nov-97	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 90 CT	GRA0764105		Unknown	Male Adult	24-Nov-97	SWELLING	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	AKI0763976		Unknown	Female Child	24-Nov-97	DRYNESS	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 90 CT	GIR0764745	14	Year(s)	Female Child	26-Nov-97	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	PAC0764666		Unknown	Female Adult	26-Nov-97	SCRATCH	US	N	INJURY	2	Day(s)
NOX ACNE PADS REG 90 CT	EDW0764626		Unknown	Female Adult	26-Nov-97	BLISTERS	US	N	SKIN	4	Day(s)
NOX ASPTC ASTR XTR 8 OZ	NUK0765009	2	Year(s)	Female Child	01-Dec-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	QUI0765051		Unknown	Female Adult	01-Dec-97	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	SHA0765112	15	Year(s)	Female Child	01-Dec-97	REDNESS	CA	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	GUT0765172	15	Year(s)	Female Child	01-Dec-97	PIMPLES	US	N	SKIN	11	Year(s)
NOX ACNE PADS MAX 65 CT	RAY0765286	20	Year(s)	Female Adult	02-Dec-97	ACNE	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	HOS0765843	13	Year(s)	Male Child	04-Dec-97	REDNESS	US	N	SKIN	15	Minute(s)
NOX ORI PAD REG PAD NTNT 50 CT	LAU0765853	11	Year(s)	Male Child	04-Dec-97	REDNESS	CA	N	SKIN		

NOX ORI PAD REG PAD NTNT 50 CT	LAU0765853	14	Year(s)	Female Child	04-Dec-97	REDNESS	CA	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	SIF0766021		Unknown	Female Adult	05-Dec-97	BURNING	US	N	INGESTION	2	Minute(s)
NOX ACNE PADS MAX 65 CT	PIT0767132	15	Year(s)	Male Child	12-Dec-97	PIMPLES	US	N	SKIN	4	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	BEN0767291	12	Year(s)	Female Child	12-Dec-97	REDNESS	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 90 CT	RAF0767436		Unknown	Female Adult	15-Dec-97	WELTS	US	N	SKIN	3	Week(s)
NOX ASPTC ASTR REG 8 OZ	MC 0767488	3	Year(s)	Male Child	15-Dec-97	HEADACHE	US	N	INGESTION	30	Minute(s)
NOX ACNE PADS MAX 65 CT	DRO0768021		Unknown	Female Child	17-Dec-97	ACNE	US	N	SKIN	4	Month(s)
NOX ACNE PADS MAX 65 CT	GUA0767865	13	Year(s)	Female Child	17-Dec-97	REDNESS	US	N	SKIN	24	Hour(s)
NOX ACNE PADS REG 65 CT	PUC0768036	14	Year(s)	Female Child	17-Dec-97	HIVES	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	LEO0767841	14	006	Male Child	17-Dec-97	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	BUG0768473	13	Year(s)	Female Child	22-Dec-97	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	NEW0768793	38	Year(s)	Female Adult	23-Dec-97	SWELLING	US	N	SKIN	4	Day(s)
NOX ACNE PADS MAX 65 CT	GRO0769207	15	Year(s)	Female Child	29-Dec-97	RASH	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	COX0769107	13	Year(s)	Female Child	29-Dec-97	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	CAU0769668	16	Year(s)	Male Child	31-Dec-97	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	FIS0769638	12	Year(s)	Female Child	31-Dec-97	STINGING	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DAV0769631	14	Year(s)	Male Child	31-Dec-97	DRYNESS	US	N	SKIN	1	Month(s)
NOX ASPTC ASTR REG 8 OZ	JON0769911		Unknown	Unknown	02-Jan-98	ACNE	US	N	SKIN	1.5	Month(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	FRA0770418	16	Year(s)	Male Adult	06-Jan-98	NONE	US	N	INGESTION		
NOXZEMA PADS MAXIMUM STRENGTH ND	HAR0770859	12	Year(s)	Female Child	07-Jan-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	ZUC0771054		Unknown	Female Adult	08-Jan-98	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	DUG0771238	36	Year(s)	Female Adult	09-Jan-98	BURNING	US	N	SKIN	5	Day(s)
NOX ACNE PADS REG 65 CT	TUS0771199		Unknown	Female Adult	09-Jan-98	RASH	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 90 CT	LEW0771669		Unknown	Male Adult	12-Jan-98	DRYNESS	US	N	SKIN	10	Day(s)
NOX ACNE PADS MAX 90 CT	COR0771856	21	Year(s)	Male Adult	13-Jan-98	ACNE	US	N	SKIN	10	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	TAG0771704	27	Year(s)	Female Adult	13-Jan-98	BURNING	CA	N	SKIN		
D-NOX PADS REG STR ND	JOR0772077	31	Year(s)	Female Adult	14-Jan-98	BURNING	CA	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	DEN0772346	13	Year(s)	Female Child	15-Jan-98	PEELING	US	N	SKIN	10	Day(s)
NOX ACNE PADS MAX 65 CT	WAT0772333	17	Year(s)	Female Adult	15-Jan-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	JIW0772360	21	Unknown	Male Adult	15-Jan-98	RASH	CA	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	PAL0772588	14	Year(s)	Male Child	16-Jan-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SAM0773189	16	Year(s)	Male Child	21-Jan-98	DISCOLORATION	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	GLI0773431	35	Year(s)	Male Adult	22-Jan-98	REDNESS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	ROB0773319		Unknown	Unknown	22-Jan-98	HIVES	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	SNY0773775	16	Year(s)	Male Child	26-Jan-98	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SNY0773775		Unknown	Female Adult	26-Jan-98	BURNING	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 90 CT	BUR0774256	16	Year(s)	Female Child	27-Jan-98	PIMPLES	US	N	SKIN	1	Month(s)

NOXZEMA PADS MAXIMUM STRENGTH ND	DIS0774156		Unknown	Unknown	27-Jan-98	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	LEH0774402		Unknown	Female Adult	28-Jan-98	REDNESS	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	ROG0774458	16	Year(s)	Male Child	28-Jan-98	ACNE	US	N	SKIN		
NOX ACNE PADS REG 90 CT	HAN0774581	18	Year(s)	Female Adult	28-Jan-98	RASH	US	N	SKIN	1	Week(s)
NOX ORI PAD REG PAD NTNT 50 CT	CLA0774774	22	Year(s)	Female Adult	29-Jan-98	PIMPLES	CA	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	BAX0774959	16	Year(s)	Female Adult	30-Jan-98	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	GAS0775397	21	Year(s)	Female Adult	02-Feb-98	BURNING	US	N	SKIN	5	Minute(s)
NOX ACNE PADS MAX 65 CT	MUH0775521	20	Year(s)	Female Adult	03-Feb-98	PIMPLES	US	N	SKIN	4	Day(s)
NOX ASPTC ASTR REG 8 OZ	ROB0775664	13	Year(s)	Female Child	03-Feb-98	REDNESS	US	N	SKIN	1.5	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	ALK0775563		Unknown	Female Adult	03-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	PAW0775693	14	Year(s)	Female Child	03-Feb-98	ACNE	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	DIA0776190		Unknown	Unknown	06-Feb-98	PEELING	US	N	SKIN	1	Day(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	DIR0776406	60	Year(s)	Female Adult	09-Feb-98	SORES	CA	Y	SKIN		
NOX ACNE PADS MAX 65 CT	ERV0776590		Unknown	Male Adult	09-Feb-98	REDNESS	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	COC0776432		Unknown	Female Adult	09-Feb-98	RASH	CA	N	SKIN	10	Minute(s)
NOX ACNE PADS MAX 65 CT	HUT0776881		Unknown	Female Adult	10-Feb-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	GAT0777150	15	Year(s)	Male Adult	11-Feb-98	PIMPLES	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	MOH0777032	15	Year(s)	Female Child	11-Feb-98	BURNING	CA	N	EYE	5	Minute(s)
NOX ACNE PADS MAX 65 CT	SEM0777339	21	Year(s)	Female Adult	12-Feb-98	BUMPS	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	PHI0777323		Unknown	Female Adult	12-Feb-98	RASH	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	WOJ0777269		Unknown	Female Adult	12-Feb-98	REDNESS	US	N	SKIN		Unknown
NOX ASPTC ASTR XTR 8 OZ	HEM0777472		Unknown	Female Adult	13-Feb-98	REDNESS	US	N	SKIN		
D-NOX PADS REG STR ND	MOR0777605	12	Year(s)	Female Child	16-Feb-98	STINGING	CA	N	SKIN	20	Minute(s)
NOX ORI PAD REG PAD NTNT 75 CT	MOR0777914		Unknown	Male Adult	17-Feb-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SAW0778168		Unknown	Female Adult	18-Feb-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	MEL0778211	19	Year(s)	Female Adult	19-Feb-98	BUMPS	US	Y	SKIN	2	Week(s)
D-NOX PADS REG STR ND	WIL0778492	47	Year(s)	Female Adult	20-Feb-98	REDNESS	CA	N	EYE	5	Hour(s)
NOX ACNE PADS MAX 65 CT	BAR0778651	13	Year(s)	Female Child	20-Feb-98	STINGING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	NEW0778776		Unknown	Female Adult	23-Feb-98	HIVES	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	MOO0779181	30	Year(s)	Female Adult	24-Feb-98	BUMPS	US	N	SKIN	2	Day(s)
D-NOX PADS REG STR ND	IRV0779295	38	Year(s)	Female Adult	25-Feb-98	REDNESS	CA	N	SKIN		
D-NOX PADS REG STR ND	MOR0779406	14	Year(s)	Female Child	25-Feb-98	BURNING	CA	N	SKIN		
NOX ACNE PADS MAX 90 CT	BUD0779243		Unknown	Female Adult	25-Feb-98	REDNESS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	LOP0779436		Unknown	Female Adult	25-Feb-98	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	NIE0779449	14	Year(s)	Male Child	25-Feb-98	PIMPLES	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	SHE0779282	16	Year(s)	Male Child	25-Feb-98	SWELLING	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	DAV0779644	11	Year(s)	Female Child	26-Feb-98	NONE	US	N	INGESTION		

NOXZEMA PADS MAXIMUM STRENGTH ND	SAD0779664		Unknown	Unknown	26-Feb-98	BURNING	US	N	SKIN	1	Hour(s)
NOX ACNE PADS MAX 65 CT	KOS0779768	15	Year(s)	Female Child	27-Feb-98	RASH	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SAU0779721		Unknown	Male Adult	27-Feb-98	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	WES0780206	40	Year(s)	Male Adult	02-Mar-98	TEARING	US	N	EYE INDIRECT	1	Hour(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	KIN0780305	30	006	Female Child	03-Mar-98	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 90 CT	BAT0780505	25	Year(s)	Female Adult	03-Mar-98	PIMPLES	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	AIT0780314	12	Year(s)	Female Child	03-Mar-98	RASH	CA	N	SKIN		
NOX ACNE PADS MAX 65 CT	GAL0780738		Unknown	Female Child	04-Mar-98	PIMPLES	US	N	SKIN		Unknown
NOX ACNE PADS REG 65 CT	WRI0780561		Unknown	Male Adult	04-Mar-98	BURNING	US	N	SKIN	5	Day(s)
NOX ASPTC ASTR REG 8 OZ	HIN0781534	13	Year(s)	Female Child	09-Mar-98	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	SEV0781846	13	Year(s)	Female Child	10-Mar-98	PIMPLES	US	N	SKIN	3	Week(s)
NOX ACNE PADS MAX 65 CT	BER0781976	28	Year(s)	Male Adult	11-Mar-98	RASH	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	ASA0782093	12	Year(s)	Female Child	11-Mar-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	SEU0782117	14	Year(s)	Female Child	11-Mar-98	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 90 CT	WIL0782035	10	Year(s)	Female Child	11-Mar-98	PIMPLES	US	N	SKIN		Day(s)
NOX ACNE PADS MAX 65 CT	EAR0782442	14	Year(s)	Female Child	13-Mar-98	ACNE	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 65 CT	FIN0782624	17	Year(s)	Female Adult	13-Mar-98	REDNESS	US	N	SKIN	10	Minute(s)
NOX ACNE PADS REG 65 CT	WAL0782514		Unknown	Female Adult	13-Mar-98	REDNESS	US	N	SKIN	5	Day(s)
NOX ACNE PADS REG 90 CT	BEL0782607	12	Year(s)	Female Child	13-Mar-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	CUE0782629	2	Year(s)	Male Child	13-Mar-98	NONE	US	N	INGESTION		
NOXZEMA PADS MAXIMUM STRENGTH ND	PAT0782639		Unknown	Female Adult	13-Mar-98	BURNING	US	N	SKIN		Minute(s)
NOX ORI PAD MAX PAD NTNT 50 CT	SME0782948		Unknown	Female Adult	16-Mar-98	REDNESS	US	N	SKIN	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	CAL0783127	15	Year(s)	Female Child	17-Mar-98	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	WYA0783273	15	Year(s)	Female Adult	17-Mar-98	NAUSEA	US	N	INHALATION		
NOX ACNE PADS MAX 90 CT	CAR0783030		Unknown	Female Adult	17-Mar-98	CRACKING	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	SAW0783990	4	Year(s)	Male Child	20-Mar-98	NONE	US	N	INGESTION		
NOX ASPTC ASTR REG 8 OZ	WIL0783944	19	006	Male Child	20-Mar-98	NONE	US	N	INGESTION		
NOX ACNE PADS REG 90 CT	JOI0784656	18	Year(s)	Male Child	24-Mar-98	RASH	US	N	SKIN	1	Week(s)
NOX ORI PAD REG PAD NTNT 50 CT	CLA0784610	15	Year(s)	Female Child	24-Mar-98	ACNE	CA	N	SKIN	6	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	LAB0784847		Unknown	Female Adult	25-Mar-98	RAW	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	PRA0785359	16	Year(s)	Male Adult	27-Mar-98	ACNE	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 65 CT	SIN0785660	17	Year(s)	Male Adult	30-Mar-98	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	SMI0785655	12	Year(s)	Female Child	30-Mar-98	REDNESS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	DAM0785647	1	Year(s)	Male Child	30-Mar-98	NONE	US	N	INGESTION		
D-NOX PADS REG STR ND	CAB0786009		Year(s)	Male Child	01-Apr-98	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	BOH0786033	17	Year(s)	Female Adult	01-Apr-98	BUMPS	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	SPA0785913		Unknown	Female Adult	01-Apr-98	SWELLING	US	N	SKIN		

NOX ASPTC ASTR REG 8 OZ	BEN0786063	13	Year(s)	Female Child	01-Apr-98	RASH	CA	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	WAT0786205	17	Year(s)	Male Adult	02-Apr-98	SWELLING	US	Y	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	LOP0786146	35	Year(s)	Female Adult	02-Apr-98	BUMPS	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 90 CT	JAN0786641		Unknown	Female Adult	06-Apr-98	REDNESS	US	N	SKIN	6	Hour(s)
NOX ORI PAD MAX PAD NTNT 50 CT	STE0786793	59	Year(s)	Male Adult	06-Apr-98	IRRITATION	US	N	INHALATION	1	Month(s)
NOX ORI PAD REG PAD NTNT 50 CT	MAC0786697	18	Year(s)	Female Adult	06-Apr-98	REDNESS	CA	N	SKIN	7	Hour(s)
NOX ACNE PADS MAX 65 CT	KOT0787082	11	Year(s)	Female Child	07-Apr-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	MAP0787060		Unknown	Female Adult	07-Apr-98	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	WAT0787051		Unknown	Female Child	07-Apr-98	DRYNESS	US	N	SKIN		Unknown
NOX ORI PAD REG PAD NTNT 50 CT	PAR0787114	10	Year(s)	Female Child	07-Apr-98	BURNING	US	N	SKIN	4	Day(s)
NOX ACNE PADS REG 65 CT	LUP0787169		Unknown	Female Adult	08-Apr-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS REG 90 CT	CRU0787191		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR REG 8 OZ	MOS0787151		Unknown	Female Adult	08-Apr-98	TINGLING	US	N	SKIN		Minute(s)
NOX ASPTC ASTR XTR 8 OZ	ROD0787311	17	Year(s)	Female Child	08-Apr-98	ACNE	US	N	SKIN	1	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	JAG0787145		Unknown	Female Adult	08-Apr-98	PIMPLES	US	N	SKIN	4	Day(s)
NOX ASPTC ASTR REG 8 OZ	MAX0787571		Unknown	Female Adult	09-Apr-98	REDNESS	US	N	SKIN	4	Month(s)
NOX ACNE PADS MAX 90 CT	CHE0787886	11	Year(s)	Female Child	13-Apr-98	PIMPLES	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	BUT0787870		Unknown	Female Adult	13-Apr-98	RASH	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	TER0788237	14	Year(s)	Female Child	14-Apr-98	PIMPLES	US	N	SKIN	4	Day(s)
D-NOX PADS REG STR ND	STO0788529		Unknown	Female Adult	15-Apr-98	ACNE	US	Y	SKIN		
NOX ASPTC ASTR REG 8 OZ	SCA0788840	17	Year(s)	Male Child	17-Apr-98	REDNESS	US	N	SKIN	4	Day(s)
NOX ACNE PADS MAX 90 CT	BUR0789287	17	Year(s)	Female Child	20-Apr-98	BUMPS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	MOS0789282	12	Year(s)	Female Child	20-Apr-98	DIFFICULTY	US	N	INHALATION		
NOX ACNE PADS REG 65 CT	BRO0789569	13	Year(s)	Female Child	21-Apr-98	BURN	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LAN0789568	13	Year(s)	Female Child	21-Apr-98	RASH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	CHI0790039		Unknown	Female Adult	23-Apr-98	SCRATCH	US	N	INJURY	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CHI0790107		Unknown	Female Adult	24-Apr-98	SCRATCH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	ALU0790507		Unknown	Male Adult	27-Apr-98	REDNESS	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	HOM0790935		Unknown	Female Child	29-Apr-98	ACNE	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	KOR0790974		Unknown	Female Adult	29-Apr-98	RASH	US	N	SKIN	10	Minute(s)
NOX ASPTC ASTR XTR 8 OZ	MIZ0791888	18	006	Female Child	04-May-98	NONE	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	ADS0791822	14	Year(s)	Female Child	04-May-98	REDNESS	CA	N	SKIN	5	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	MIS0791735	18	Year(s)	Female Adult	04-May-98	RASH	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	BLE0791969	23	Year(s)	Female Adult	05-May-98	NAUSEA	US	N	INGESTION	3.5	Hour(s)
NOX ASPTC ASTR REG 8 OZ	MUS0791999	17	Unknown	Male Child	05-May-98	STOMACHACHE	US	N	INHALATION		
NOX ORI PAD MAX PAD NTNT 50 CT	STA0792155	13	Year(s)	Female Child	05-May-98	ACNE	US	N	SKIN	2	Week(s)
NOX ACNE PADS REG 65 CT	DUR0792583	13	Year(s)	Female Child	07-May-98	BURNING	US	N	SKIN		

NOX ORI PAD REG PAD NTNT 50 CT	AL-0792688	18	Year(s)	Female Child	08-May-98	RASH	US	N	SKIN	4	Day(s)
D-NOX PADS REG STR ND	CLO0793063	14	Year(s)	Female Child	11-May-98	PIMPLES	US	N	SKIN	1	Month(s)
NOX ACNE PADS MAX 65 CT	COS0792865	17	Year(s)	Female Child	11-May-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WOO0793059	15	Year(s)	Female Child	11-May-98	DISCOLORATION	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	FRA0793034		Unknown	Female Child	11-May-98	BLISTERS	US	N	SKIN		
NOX ACNE PADS REG 90 CT	KAO0792892	22	Year(s)	Male Adult	11-May-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	CRA0793229	19	Year(s)	Male Adult	12-May-98	PIMPLES	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	KLA0793208	12	Year(s)	Male Child	12-May-98	REDNESS	US	N	SKIN	11	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	DAV0793280	11	Year(s)	Female Child	12-May-98	ITCHING	US	N	SKIN	5	Day(s)
D-NOX PADS REG STR ND	LAR0793428	14	Year(s)	Female Child	13-May-98	REDNESS	CA	N	SKIN		
NOX ACNE PADS MAX 90 CT	BYE0793623		Unknown	Unknown	14-May-98	RASH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	KIS0793802	14	Year(s)	Female Adult	15-May-98	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	HAU0793819	16	Year(s)	Female Child	15-May-98	PIMPLES	US	N	SKIN	1	Week(s)
D-NOX PADS REG STR ND	AVE0794328	15	Year(s)	Unknown	19-May-98	LACK OF EFFICACY	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 90 CT	STE0794228		Unknown	Unknown	19-May-98	SCRATCH	US	N	INJURY	3	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	RIT0794194	16	Year(s)	Female Child	19-May-98	REDNESS	US	N	SKIN		Day(s)
NOX ACNE PADS MAX 65 CT	NAS0794514	13	Year(s)	Female Child	20-May-98	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	NAV0794404	15	Year(s)	Male Child	20-May-98	IRRITATION	US	N	SKIN	10	Minute(s)
NOX ORI PAD REG PAD NTNT 50 CT	NGO0794524	14	Year(s)	Female Child	20-May-98	REDNESS	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	ROM0794574	16	Year(s)	Female Child	21-May-98	VOMITING	US	N	INGESTION	2	Hour(s)
NOX ORI PAD REG PAD NTNT 75 CT	GEL0794899		Unknown	Unknown	22-May-98	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	ODO0796006	2	Year(s)	Male Child	01-Jun-98	NONE	US	N	INGESTION		
NOX ACNE PADS REG 90 CT	KAU0796443		Unknown	Female Adult	03-Jun-98	BURNING	US	N	EYE INDIRECT		
D-NOX PADS REG STR ND	JOE0796646	1	Year(s)	Female Child	04-Jun-98	NONE	US	N	INGESTION		
NOXZEMA PADS MAXIMUM STRENGTH ND	LIS0796632	13	Year(s)	Male Child	04-Jun-98	PIMPLES	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 90 CT	MAR0796800	15	Year(s)	Female Child	05-Jun-98	BRUISE	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SEE0797207	14	Year(s)	Female Adult	08-Jun-98	FLAKING	US	N	SKIN	2	Week(s)
NOX ORI PAD MAX PAD NTNT 50 CT	LES0797234		Unknown	Female Adult	08-Jun-98	REDNESS	US	Y	SKIN	1	Week(s)
D-NOX PADS REG STR ND	CUR0797310		Unknown	Female Child	09-Jun-98	STINGING	US	N	EYE INDIRECT		
NOX ASPTC ASTR REG 8 OZ	CRU0797678	17	Year(s)	Female Child	10-Jun-98	HAIR LOSS (DIFFUSE)	US	N	SKIN	3	Week(s)
NOX ACNE PADS REG 90 CT	JOH0797841	14	Year(s)	Female Child	11-Jun-98	RASH	US	N	SKIN	1	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	ROB0797764	17	Year(s)	Female Child	11-Jun-98	BUMPS	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 65 CT	CHA0797980	19	Year(s)	Female Adult	12-Jun-98	BURNING	US	N	SKIN		
NOX ACNE PADS REG 90 CT	SMI0798089	25	Year(s)	Female Adult	12-Jun-98	REDNESS	US	N	SKIN	24	Hour(s)
NOX ASPTC ASTR REG 8 OZ	WIL0798227	29	Year(s)	Female Adult	15-Jun-98	ITCHING	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	ORE0798328	18	Year(s)	Female Adult	15-Jun-98	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	AAR0798535	14	Year(s)	Male Child	16-Jun-98	BUMPS	US	N	SKIN		

NOX ACNE PADS MAX 90 CT	SMI0798746		Unknown	Female Adult	17-Jun-98	SCRATCH	US	N	INJURY	1	Day(s)
NOX ACNE PADS REG 65 CT	HOV0798724		Unknown	Female Adult	17-Jun-98	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	UNK0799018		Unknown	Unknown	18-Jun-98	ACNE	US	N	SKIN		
NOX ACNE PADS REG 65 CT	PEP0798942	13	Year(s)	Female Child	18-Jun-98	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	CHA0798974	16	Year(s)	Female Adult	18-Jun-98	REDNESS	US	N	SKIN		
D-NOX PADS REG STR ND	ALV0799229		Unknown	Female Adult	22-Jun-98	PEELING	US	N	SKIN	2	Day(s)
D-NOX PADS REG STR ND	REF0799486		Unknown	Female Child	22-Jun-98	RASH	US	N	SKIN		
D-NOX PADS REG STR ND	ROS0799509	13	Year(s)	Female Child	22-Jun-98	ACNE	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	YOU0799510	14	Year(s)	Female Child	22-Jun-98	STINGING	US	N	SKIN		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	GRO0799566	37	Year(s)	Female Adult	23-Jun-98	REDNESS	CA	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	MC 0799678	80	Year(s)	Female Adult	23-Jun-98	STINGING	CA	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	WIL0800118		Unknown	Male Adult	25-Jun-98	REDNESS	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 50 CT	BOB0800042	22	Year(s)	Male Adult	25-Jun-98	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	SAV0800316		Unknown	Female Adult	26-Jun-98	BURNING	US	N	SKIN		Unknown
NOX ACNE PADS MAX 65 CT	MUE0800507		Unknown	Female Adult	29-Jun-98	IRRITATION	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LYN0800523	34	Year(s)	Female Adult	29-Jun-98	BURNING	US	Y	SKIN		Unknown
D-NOX PADS REG STR ND	GRA0800769		Unknown	Female Adult	30-Jun-98	ITCHING	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	ROG0800792	12	Year(s)	Female Child	30-Jun-98	BAD TASTE IN MOUTH	US	N	INGESTION		
NOX ORI PAD REG PAD NTNT 50 CT	HUR0800874	11	Unknown	Female Child	30-Jun-98	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR REG 4 OZ	QUI0801020	24	006	Male Child	01-Jul-98	NONE	US	N	INGESTION		
NOXZEMA PADS MAXIMUM STRENGTH ND	BOO0801123	34	Year(s)	Female Adult	01-Jul-98	PIMPLES	US	N	SKIN	2	Week(s)
D-NOX PADS REG STR ND	SCH0801368	13	Year(s)	Female Child	03-Jul-98	ITCHING	CA	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	GUT0801461		Unknown	Female Adult	06-Jul-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	ABR0801388	11	Year(s)	Female Child	06-Jul-98	PIMPLES	US	N	SKIN		Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	KER0801663		Unknown	Female Child	06-Jul-98	RASH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	ALL0801898	17	Year(s)	Male Child	07-Jul-98	TIGHTNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WOO0801889	14	Year(s)	Female Child	07-Jul-98	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	GUZ0802343	14	Year(s)	Female Adult	09-Jul-98	REDNESS	US	N	SKIN	2	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	CRI0802451		Unknown	Female Adult	09-Jul-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	BEN0802938	15	Year(s)	Female Adult	13-Jul-98	ACNE	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	MCK0803370	14	Unknown	Female Child	14-Jul-98	BUMPS	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CAT0803207		Unknown	Female Adult	14-Jul-98	TIGHTNESS	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	CAL0803445	13	Year(s)	Male Child	15-Jul-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	MAL0803620	13	Year(s)	Female Child	15-Jul-98	ACNE	US	N	SKIN		
NOX ACNE PADS REG 90 CT	MAL0803619	16	Year(s)	Female Child	15-Jul-98	ACNE	US	N	SKIN		
NOX ACNE PADS REG 90 CT	STO0803648		Unknown	Female Adult	16-Jul-98	REDNESS	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	HEB0804177	13	Year(s)	Female Child	17-Jul-98	DRYNESS	US	N	SKIN		

NOXZEMA PADS MAXIMUM STRENGTH ND	HUG0804102	13	Year(s)	Female Child	17-Jul-98	STINGING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	COS0804415	12	Year(s)	Female Child	20-Jul-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	BRO0804553	11	Year(s)	Male Child	21-Jul-98	PIMPLES	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	PAR0804676		Unknown	Female Adult	21-Jul-98	DRYNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	CLE0804739		Unknown	Female Adult	21-Jul-98	REDNESS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	BAT0804578	12	Year(s)	Female Child	21-Jul-98	PIMPLES	US	N	SKIN		Unknown
NOX ACNE PADS MAX 65 CT	DRA0804990		Unknown	Female Child	22-Jul-98	STINGING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	VAN0805149	15	Year(s)	Female Child	23-Jul-98	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	SAL0805972	18	Unknown	Female Adult	27-Jul-98	BURNING	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	DAR0805975	27	Year(s)	Female Adult	27-Jul-98	PIMPLES	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	JAE0806113		Unknown	Female Adult	28-Jul-98	BUMPS	US	N	SKIN	8	Day(s)
NOX ACNE PADS MAX 90 CT	GRA0806542	73	Year(s)	Male Adult	29-Jul-98	BUMPS	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	MUR0806460		Unknown	Unknown	29-Jul-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	PAR0806816	12	Year(s)	Female Child	30-Jul-98	PIMPLES	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	DWY0806783	15	Unknown	Female Child	30-Jul-98	BURNING	US	N	SKIN	5	Minute(s)
NOX ACNE PADS MAX 65 CT	JOH0807169		Unknown	Female Adult	03-Aug-98	RASH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	BOY0807045	16	Year(s)	Female Child	03-Aug-98	REDNESS	US	N	SKIN	12	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	FAI0807110		Unknown	Male Adult	03-Aug-98	STINGING	US	N	SKIN		
NOX ACNE PADS REG 90 CT	STA0807365	16	Year(s)	Female Child	04-Aug-98	PIMPLES	US	N	SKIN	4	Day(s)
NOX ASPTC ASTR XTR 8 OZ	KUT0807607		Unknown	Female Adult	05-Aug-98	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	HIL0807678		Unknown	Female Adult	05-Aug-98	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	BOY0808036	14	Unknown	Female Child	06-Aug-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	HIR0807868		Unknown	Female Adult	06-Aug-98	PIMPLES	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 90 CT	ROM0807995	18	Year(s)	Male Adult	06-Aug-98	PEELING	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 90 CT	RAT0807853	28	Year(s)	Female Child	06-Aug-98	SCRATCH	US	N	SKIN	2	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	RIF0807975		Unknown	Female Adult	06-Aug-98	BUMPS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	SIM0807985		Unknown	Female Adult	06-Aug-98	DRYNESS	US	N	SKIN		Unknown
NOX ORI PAD REG PAD NTNT 50 CT	NEF0808068	30	Year(s)	Female Child	06-Aug-98	PEELING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	ABU0808266	14	Year(s)	Male Child	07-Aug-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 90 CT	BOZ0808522	12	Year(s)	Female Child	10-Aug-98	PIMPLES	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	LOV0808573	43	Year(s)	Female Adult	10-Aug-98	ACNE	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	ZIM0808869		Unknown	Female Adult	11-Aug-98	SCRATCH	US	N	INJURY	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	TOM0808870	21	Year(s)	Female Adult	11-Aug-98	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	BEL0809097		Unknown	Female Child	12-Aug-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	BAL0809516		Unknown	Male Adult	14-Aug-98	BURNING	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	BIC0809606	14	Year(s)	Female Child	14-Aug-98	RASH	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	DEN0809483		Unknown	Female Adult	14-Aug-98	SCRATCH	US	N	INJURY	1	Day(s)

DISC-NOXZEMA ASTRINGENT OILY SIZE ND	DEP0809963		Unknown	Female Adult	17-Aug-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	PRI0809743		Unknown	Female Adult	17-Aug-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS REG 90 CT	ROW0810015		Unknown	Female Adult	18-Aug-98	ACNE	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	CYR0810271		Unknown	Female Adult	19-Aug-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	FUL0810442	12	Year(s)	Female Child	19-Aug-98	ACNE	US	N	SKIN	2	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	MAR0810673		Unknown	Male Adult	20-Aug-98	PIMPLES	US	N	SKIN	3	Week(s)
NOX ACNE PADS MAX 90 CT	PRA0810844	13	Year(s)	Female Adult	21-Aug-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HEH0811400	14	Year(s)	Unknown	25-Aug-98	SCRATCH	US	N	INJURY		
NOX ASPTC ASTR XTR 8 OZ	TAY0811268	18	Year(s)	Male Child	25-Aug-98	PEELING	US	N	SKIN	3	Week(s)
NOX ASPTC ASTR XTR 8 OZ	HUS0811850		Unknown	Female Adult	27-Aug-98	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	FUL0812332		Unknown	Female Adult	31-Aug-98	STINGING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	GAL0812170		Unknown	Female Adult	31-Aug-98	SORENESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	LIT0812274	12	Year(s)	Female Child	31-Aug-98	WARM	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	PUR0812226		Unknown	Female Adult	31-Aug-98	NONE	US	N	INGESTION		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	JEW0812488		Unknown	Female Adult	01-Sep-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	BUT0812503	19	Year(s)	Male Adult	01-Sep-98	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	FRO0812825		Unknown	Male Adult	02-Sep-98	PIMPLES	US	N	SKIN		Day(s)
NOX ACNE PADS REG 65 CT	MAS0812698	18	Year(s)	Female Adult	02-Sep-98	PIMPLES	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	JON0813037	43	Year(s)	Female Adult	03-Sep-98	DRYNESS	US	N	SKIN	7	Day(s)
NOX ACNE PADS MAX 65 CT	LAR0813260	15	Year(s)	Male Child	04-Sep-98	DRYNESS	US	N	SKIN	24	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	FOR0813211		Unknown	Female Adult	04-Sep-98	PEELING	US	N	SKIN		Week(s)
NOX ASPTC ASTR XTR 8 OZ	WEG0813262		Unknown	Female Adult	04-Sep-98	PIMPLES	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	KAR0813547		Unknown	Female Adult	08-Sep-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	GIN0813303	38	Year(s)	Female Adult	08-Sep-98	SCRATCH	US	N	INJURY	4	Day(s)
NOX ACNE PADS REG 65 CT	GOR0813573		Unknown	Female Child	08-Sep-98	PIMPLES	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 90 CT	WIS0813707	26	Year(s)	Female Adult	09-Sep-98	REDNESS	US	N	SKIN	8	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	KER0813651	12	Year(s)	Female Child	09-Sep-98	DISCOLORATION	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 90 CT	WAL0813787	23	Year(s)	Male Adult	10-Sep-98	PEELING	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	GRU0814027		Unknown	Female Adult	11-Sep-98	CUT	US	N	INJURY		Minute(s)
NOX ACNE PADS MAX 65 CT	HEN0814448	13	Year(s)	Female Child	14-Sep-98	BUMPS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	PAS0814216	13	Year(s)	Female Child	14-Sep-98	SCRATCH	US	N	INJURY	3.5	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	GLA0814234		Unknown	Female Adult	14-Sep-98	PIMPLES	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 90 CT	ROD0814679		Unknown	Female Adult	15-Sep-98	SCRATCH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	PAT0814870	29	Year(s)	Male Adult	16-Sep-98	RASH	CA	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	RIC0814808	15	Year(s)	Female Child	16-Sep-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WAD0814864	15	Year(s)	Male Child	16-Sep-98	ITCHING	US	N	SKIN	7	Hour(s)
NOX ACNE PADS REG 65 CT	REF0814805		Unknown	Unknown	16-Sep-98	STINGING	US	N	SKIN		

NOX ASPTC ASTR XTR 8 OZ	BAI0814878		Unknown	Female Adult	16-Sep-98	PEELING	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	HIG0814971	36	Year(s)	Female Adult	17-Sep-98	REDNESS	US	Y	SKIN	2	Month(s)
NOX ACNE PADS MAX 65 CT	JON0814920	15	Year(s)	Male Child	17-Sep-98	ACNE	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	REY0814936	40	Year(s)	Female Adult	17-Sep-98	RASH	CA	N	SKIN	3	Week(s)
NOX ASPTC ASTR XTR 8 OZ	HER0814899	13	Year(s)	Female Child	17-Sep-98	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	CAR0815479	14	Year(s)	Female Child	21-Sep-98	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	BYN0815621		Unknown	Female Adult	22-Sep-98	SCRATCH	US	N	SKIN	4	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	BOT0815638		Unknown	Female Adult	22-Sep-98	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	ONC0815698		Unknown	Female Adult	22-Sep-98	REDNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	BOT0815639		Unknown	Female Adult	22-Sep-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	LOV0815782		Unknown	Female Adult	23-Sep-98	BURNING	US	N	SKIN	45	Minute(s)
NOX ASPTC ASTR REG 8 OZ	STR0816439	5	Year(s)	Male Child	28-Sep-98	VOMITING	US	N	INGESTION	20	Minute(s)
NOX ASPTC ASTR XTR 8 OZ	BRO0816551	2	Year(s)	Male Child	28-Sep-98	NONE	US	N	INGESTION		
D-NOX PADS REG STR ND	GRI0816780	21	Year(s)	Female Adult	29-Sep-98	STINGING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	HER0816947		Unknown	Female Child	30-Sep-98	ACNE	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CHR0816820	9	006	Female Child	30-Sep-98	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 90 CT	MC 0817611	13	Unknown	Female Child	05-Oct-98	REDNESS	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	CAS0817800	16	001	Male Adult	06-Oct-98	IRRITATION	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	HAN0817820	12	Year(s)	Female Child	06-Oct-98	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 75 CT	HIN0817840	14	Year(s)	Male Child	06-Oct-98	ACNE	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	BRO0818054		Unknown	Male Adult	07-Oct-98	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	REF0818264		Unknown	Female Adult	08-Oct-98	BURNING	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	QUA0818210	15	Year(s)	Unknown	08-Oct-98	REDNESS	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	HIL0818504		Unknown	Female Adult	12-Oct-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	VAN0818814		Unknown	Female Adult	13-Oct-98	DRYNESS	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	DAL0818878	13	Year(s)	Male Child	13-Oct-98	RASH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	VAN0819203		Unknown	Female Adult	15-Oct-98	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	JAR0819662		Unknown	Female Adult	19-Oct-98	TEARING	US	N	EYE INDIRECT		
NOX ASPTC ASTR XTR 8 OZ	AME0819539		Unknown	Female Adult	19-Oct-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	GUN0819546		Unknown	Female Adult	19-Oct-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	MAR0819989		Unknown	Female Adult	20-Oct-98	DRYNESS	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	DEV0819926		Unknown	Female Adult	20-Oct-98	REDNESS	US	N	SKIN	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SAC0820124	42	Year(s)	Female Adult	21-Oct-98	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	DEJ0820442	25	Year(s)	Female Adult	22-Oct-98	SCRATCH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	KIN0820463		Unknown	Female Adult	22-Oct-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR REG 8 OZ	MUL0820303			Female Adult	22-Oct-98	PEELING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	NG0820584		Unknown	Unknown	23-Oct-98	SHORT OF BREATH	US	N	INHALATION		

DISC-NOXZEMA ASTRINGENT OILY SIZE ND	HEA0820805		Unknown	Female Adult	26-Oct-98	DRYNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	SAL0820799	20	Year(s)	Female Adult	26-Oct-98	RASH	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	LEE0821294	14	Year(s)	Male Child	28-Oct-98	PIMPLES	US	N	SKIN	1	Week(s)
D-NOX PADS REG STR ND	SMI0821440	33	Year(s)	Female Adult	29-Oct-98	CUT	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	ANN0821590		Unknown	Female Adult	29-Oct-98	DISCOLORATION	US	N	SKIN	8	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	HOO0821444	16	Year(s)	Female Child	29-Oct-98	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	HOL0821783	13	Year(s)	Female Child	30-Oct-98	BURNING	US	N	SKIN	3	Day(s)
NOX ASPTC ASTR XTR 8 OZ	PEC0821836	28	Year(s)	Female Adult	02-Nov-98	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BYE0822350		Unknown	Female Adult	03-Nov-98	RASH	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	FLO0822295	16	Year(s)	Male Child	03-Nov-98	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	UNK0822359	3	Year(s)	Female Child	03-Nov-98	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	JAE0822273		Unknown	Unknown	03-Nov-98	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	WON0822740	13	Year(s)	Female Child	05-Nov-98	BUMPS	CA	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BUR0822730		Unknown	Female Adult	05-Nov-98	NONE	US	N	INGESTION		
NOX ACNE PADS REG 90 CT	CHA0823352		Unknown	Female Adult	09-Nov-98	SCRATCH	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	MC 0823081		Unknown	Male Adult	09-Nov-98	STINGING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MOS0823185	11	Year(s)	Female Child	09-Nov-98	ACNE	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 90 CT	WHI0823472	40	Year(s)	Female Adult	10-Nov-98	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	CHR0823592		Unknown	Female Adult	10-Nov-98	SWELLING	US	N	SKIN	11	Day(s)
NOX ACNE PADS REG 65 CT	QUI0823948	18	Year(s)	Female Adult	12-Nov-98	ACNE	CA	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	KRO0823889	64	Year(s)	Female Adult	12-Nov-98	BURNING	US	N	SKIN	3	Minute(s)
NOX ASPTC ASTR XTR 8 OZ	BER0824361	30	Year(s)	Female Adult	16-Nov-98	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	RIT0824801	32	Year(s)	Female Adult	17-Nov-98	SCRATCH	US	N	INJURY	8	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	SPA0824846	32	Year(s)	Female Adult	17-Nov-98	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	WEL0825037		Unknown	Female Child	18-Nov-98	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	LON0824974	11	Year(s)	Female Child	18-Nov-98	HAIR LOSS (DIFFUSE)	CA	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	SMI0825489	39	Year(s)	Female Adult	20-Nov-98	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SIN0825526		Unknown	Female Adult	23-Nov-98	DRYNESS	US	N	SKIN	1	Month(s)
NOX ACNE PADS REG 65 CT	WAT0826037		Unknown	Female Adult	24-Nov-98	BUMPS	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	DUG0826096		Unknown	Female Adult	25-Nov-98	STINGING	US	N	SKIN	5	Minute(s)
NOX ACNE PADS MAX 90 CT	MAR0826821	29	Year(s)	Female Adult	01-Dec-98	SCRATCH	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	CON0827706	23	Year(s)	Female Adult	07-Dec-98	PIMPLES	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	SNE0827610	29	Year(s)	Female Adult	07-Dec-98	DRYNESS	CA	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	KEN0827952		Unknown	Female Adult	08-Dec-98	BUMPS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	ULI0827892		Unknown	Female Adult	08-Dec-98	BLISTERS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	SMA0828310		Unknown	Female Adult	10-Dec-98	DISCOLORATION	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	MC 0829252	52	Year(s)	Female Adult	16-Dec-98	(GENERALIZED)	US	N	ORAL/NASAL	5	Minute(s)

NOX ACNE PADS MAX 65 CT	DOY0829474	40	Year(s)	Female Adult	17-Dec-98	SCRATCH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	WAT0829519	37	Year(s)	Female Adult	17-Dec-98	DRYNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	BEN0830136		Unknown	Female Adult	22-Dec-98	SWELLING	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	DER0831095	12	Year(s)	Female Child	30-Dec-98	DRYNESS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	DER0831098		Unknown	Female Child	30-Dec-98	DRYNESS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	MUL0830955	6	Year(s)	Male Adult	30-Dec-98	VOMITING	US	N	INGESTION	3	Day(s)
NOX ACNE PADS MAX 65 CT	GAL0831119	25	Year(s)	Female Adult	31-Dec-98	BURNING	CA	N	SKIN	3	Minute(s)
NOX ASPTC ASTR REG 8 OZ	GOE0831441		Unknown	Female Adult	04-Jan-99	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR REG 8 OZ	MIC0831258		Unknown	Female Adult	04-Jan-99	ACNE	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	BEN0831432	16	Year(s)	Male Child	04-Jan-99	RASH	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	QUE0831435	14	Year(s)	Male Child	04-Jan-99	REDNESS	US	N	SKIN	6	Hour(s)
NOX ACNE PADS REG 90 CT	COL0831944	14	Year(s)	Female Child	06-Jan-99	PIMPLES	US	N	SKIN	4	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BRO0832160	15	Year(s)	Female Child	07-Jan-99	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	WEB0832226		Unknown	Female Adult	07-Jan-99	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	AND0832777	20	Year(s)	Female Adult	11-Jan-99	SCRATCH	US	N	INJURY		
NOXZEMA PADS MAXIMUM STRENGTH ND	ANT0832796	23	Year(s)	Female Adult	11-Jan-99	SCRATCH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	GUT0833039	15	Year(s)	Unknown	12-Jan-99	DRYNESS	US	N	SKIN	3	Week(s)
NOX ACNE PADS MAX 90 CT	LEC0832980		Unknown	Unknown	12-Jan-99	SCRATCH	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR REG 8 OZ	SAV0832929		Unknown	Female Adult	12-Jan-99	RASH	US	N	SKIN	1	Week(s)
NOX ACNE PADS REG 65 CT	BOY0833472	33	Year(s)	Female Adult	15-Jan-99	REDNESS	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	COF0833975		Unknown	Unknown	19-Jan-99	PIMPLES	US	N	SKIN		
NOX ACNE PADS REG 90 CT	KEI0833864	18	Year(s)	Unknown	19-Jan-99	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	SAN0834427	25	Year(s)	Male Adult	21-Jan-99	REDNESS	US	N	SKIN	10	Minute(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0834424	22	Year(s)	Male Adult	21-Jan-99	SWELLING	US	N	SKIN	15	Minute(s)
NOX ACNE PADS REG 90 CT	SMI0834636	40	Year(s)	Male Adult	22-Jan-99	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	SCH0834822		Unknown	Female Adult	25-Jan-99	IRRITATION	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BON0835412		Unknown	Female Adult	27-Jan-99	RASH	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	WAL0835512		Unknown	Female Adult	27-Jan-99	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	WEG0835498		Unknown	Female Adult	27-Jan-99	PIMPLES	US	N	SKIN	3	Week(s)
NOX ACNE PADS REG 90 CT	SAN0836851	45	Year(s)	Female Adult	03-Feb-99	RASH	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SHO0836981	19	006	Female Child	04-Feb-99	NONE	US	N	INGESTION		
NOX ACNE PADS REG 65 CT	FOG0836971		Unknown	Female Adult	04-Feb-99	REDNESS	US	N	SKIN	3	Day(s)
NOX ORI PAD REG PAD NTNT 75 CT	BRE0837082	13	Year(s)	Female Child	04-Feb-99	WELTS	US	N	EYE INDIRECT	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BEA0837246		Unknown	Female Adult	05-Feb-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	LOU0837283	18	Year(s)	Female Adult	05-Feb-99	RASH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SIM0837286		Unknown	Female Adult	05-Feb-99	WELTS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	BRA0837230		Unknown	Unknown	05-Feb-99	BURNING	US	N	SKIN		

NOX ASPTC ASTR XTR 8 OZ	LEE0837883		Year(s)	Female Adult	09-Feb-99	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	TOL0837928		Unknown	Female Adult	10-Feb-99	DRYNESS	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	HAN0838264		Unknown	Female Adult	11-Feb-99	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	PRI0838979		Unknown	Female Adult	17-Feb-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WAD0839118	22	Year(s)	Female Adult	17-Feb-99	BURNING	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	FRI0839538		Unknown	Female Adult	19-Feb-99	BURNING	US	N	SKIN		Hour(s)
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	RUS0839772	10	Year(s)	Female Child	22-Feb-99	BLISTERS	CA	Y	SKIN	2	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	BER0839729	49	Year(s)	Female Adult	22-Feb-99	CUT	US	N	INJURY	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SWE0839989		Unknown	Female Adult	23-Feb-99	BURNING	US	N	SKIN	5	Minute(s)
NOX ACNE PADS REG 65 CT	CAS0840386	17	Year(s)	Female Adult	24-Feb-99	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	COO0840736		Unknown	Female Adult	25-Feb-99	SCRATCH	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HID0840686		Unknown	Female Adult	25-Feb-99	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SMI0840834	17	Year(s)	Female Child	26-Feb-99	REDNESS	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SMI0840834		Unknown	Female Adult	26-Feb-99	REDNESS	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BIA0841292		Unknown	Female Adult	01-Mar-99	CUT	US	N	INJURY	1	Day(s)
NOX ACNE PADS REG 65 CT	DAB0841326		Unknown	Female Adult	01-Mar-99	PIMPLES	US	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	SMI0841152		Unknown	Female Adult	01-Mar-99	BURNING	US	N	SKIN	12	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SMI0841593	27	Year(s)	Female Adult	02-Mar-99	BURNING	US	N	SKIN	3	Week(s)
NOX ACNE PADS MAX 90 CT	GUT0841396	27	Year(s)	Female Adult	02-Mar-99	REDNESS	US	Y	SKIN	3	Week(s)
NOX ASPTC ASTR XTR 8 OZ	PEN0841452		Unknown	Female Adult	02-Mar-99	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HER0841875	15	Unknown	Female Child	04-Mar-99	BURNING	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	STO0842095	4	Year(s)	Male Child	04-Mar-99	NONE	US	N	ORAL/NASAL		
NOX ACNE PADS MAX 65 CT	DOT0842521	29	Year(s)	Female Adult	08-Mar-99	SCRATCH	US	N	INJURY	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	HOM0843241	13	Year(s)	Male Child	10-Mar-99	ACNE	US	N	SKIN	30	Day(s)
NOX ASPTC ASTR REG 8 OZ	MON0843461	34	Year(s)	Female Adult	11-Mar-99	BLISTERS	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	RHO0843317		Unknown	Female Adult	11-Mar-99	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	PAY0843688	16	Year(s)	Male Child	12-Mar-99	BURNING	US	N	SKIN		
NOX ASPTC ASTR REG 8 OZ	SMI0844032	8	006	Male Child	15-Mar-99	VOMITING	US	N	INGESTION		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	DAV0844525		Unknown	Female Adult	17-Mar-99	BURN	US	N	SKIN		
NOX ACNE PADS REG 65 CT	SCH0844618	13	Year(s)	Female Child	17-Mar-99	PIMPLES	CA	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	VEL0844559		Unknown	Unknown	17-Mar-99	SCRATCH	US	N	INJURY		
NOX ACNE PADS MAX 65 CT	FRE0845134		Unknown	Female Adult	19-Mar-99	SCRATCH	US	N	INJURY	2	Hour(s)
NOX ACNE PADS REG 90 CT	REC0845114	15	004	Female Child	19-Mar-99	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	FLO0844944		Unknown	Female Adult	19-Mar-99	BURNING	US	N	SKIN		
NOX ACNE PADS REG 90 CT	BUE0845483		Unknown	Female Child	22-Mar-99	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	MOO0845815	37	Year(s)	Female Adult	23-Mar-99	BURNING	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 65 CT	PAU0846428	12	Year(s)	Female Adult	26-Mar-99	BURNING	CA	N	SKIN	2	Day(s)

NOX ACNE PADS MAX 65 CT	GIS0847452	12	Year(s)	Male Child	31-Mar-99	RASH	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	SIM0848906		Unknown	Female Adult	12-Apr-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	LER0849516	19	Year(s)	Female Adult	13-Apr-99	DRYNESS	CA	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	CI 0849683		Unknown	Female Adult	14-Apr-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	ALL0849712	20	Year(s)	Male Adult	14-Apr-99	BURNING	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	SMI0850865	14	Year(s)	Female Child	20-Apr-99	ITCHING	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	MEA0851289		Unknown	Unknown	22-Apr-99	REDNESS	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	JAC0851519		Unknown	Female Child	23-Apr-99	PIMPLES	US	N	SKIN	2	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	JOH0851712	19	Year(s)	Female Adult	26-Apr-99	BURNING	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	LOM0851858		Unknown	Unknown	26-Apr-99	RASH	US	N	SKIN	1	Day(s)
NOX ACNE PADS REG 65 CT	MEI0851723		Unknown	Male Adult	26-Apr-99	DRYNESS	US	N	SKIN	4	Day(s)
NOX ASPTC ASTR XTR 8 OZ	PRO0852004		Unknown	Unknown	27-Apr-99	PIMPLES	US	N	SKIN	1	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	LYL0852208	35	Year(s)	Female Adult	28-Apr-99	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	SOU0852296	24	Year(s)	Female Adult	28-Apr-99	IRRITATION	CA	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	WIL0853312	14	Year(s)	Female Child	04-May-99	BURNING	US	N	SKIN	5	Minute(s)
NOX ACNE PADS MAX 65 CT	EAS0853560		Unknown	Female Adult	06-May-99	SCRATCH	US	N	INJURY		
NOX ORI PAD REG PAD NTNT 50 CT	NIC0853948	16	Year(s)	Female Child	07-May-99	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	PEE0853750		Unknown	Female Adult	07-May-99	PIMPLES	US	N	SKIN	1	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	DE 0855502	16	006	Female Child	17-May-99	DROWSINESS	US	N	INGESTION	15	Minute(s)
NOX ACNE PADS MAX 65 CT	MCN0855498		Unknown	Female Child	17-May-99	BUMPS	US	N	SKIN	12	Hour(s)
NOX ACNE PADS MAX 90 CT	ZEO0855399	37	Year(s)	Female Adult	17-May-99	SCRATCH	US	N	INJURY	4	Day(s)
NOX ASPTC ASTR XTR 8 OZ	GAL0855569		Unknown	Female Adult	18-May-99	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	BLO0856271		Unknown	Female Adult	21-May-99	ITCHING	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	SIE0856615		Unknown	Female Adult	24-May-99	SCRATCH	US	N	INJURY		
DISC NOXZEMA ASTRINGENT NORMAL SIZE ND	BEL0856944	39	Year(s)	Female Adult	25-May-99	BURNING	CA	N	SKIN	3	Day(s)
D-NOX PADS REG STR ND	SCH0857509	18	Year(s)	Male Adult	27-May-99	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS REG 65 CT	JOH0857466	10	Unknown	Female Child	27-May-99	STINGING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SAV0857667	40	Year(s)	Female Adult	28-May-99	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	NGU0857546	18	Year(s)	Female Adult	28-May-99	SWELLING	US	N	SKIN	3	Day(s)
NOX ACNE PADS REG 65 CT	SMI0858245	16	Year(s)	Female Adult	02-Jun-99	PIMPLES	US	N	SKIN		Unknown
NOX ORI PAD REG PAD NTNT 75 CT	GRI0858389	13	Year(s)	Male Child	03-Jun-99	RASH	US	N	SKIN	6	Day(s)
NOX ACNE PADS MAX 90 CT	MAR0858543		Unknown	Female Adult	04-Jun-99	SCRATCH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	FOL0858969	11	Year(s)	Female Child	07-Jun-99	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	RAN0859021		Unknown	Female Adult	07-Jun-99	IRRITATION	US	N	SKIN		
NOX ACNE PADS REG 65 CT	WAL0859254		Unknown	Female Adult	08-Jun-99	CUT, SCRATCH	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	MOR0859697		Unknown	Female Adult	10-Jun-99	HIVES	US	N	SKIN	2	Week(s)

NOXZEMA PADS MAXIMUM STRENGTH ND	SIL0859685	15	Year(s)	Female Child	10-Jun-99	RASH	US	N	SKIN	2	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0859651		Unknown	Unknown	10-Jun-99	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	JOH0859841	26	Year(s)	Female Adult	11-Jun-99	REDNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	NIC0859830		Unknown	Unknown	11-Jun-99	PEELING	US	N	SKIN	1	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	UNK0859836		Unknown	Unknown	11-Jun-99	BUMPS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	SOL0860408	16	Year(s)	Female Child	15-Jun-99	BURNING	US	N	SKIN	5	Day(s)
NOX ASPTC ASTR REG 8 OZ	HAT0860639	18	Year(s)	Female Adult	16-Jun-99	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	ALI0861287	19	Year(s)	Female Adult	21-Jun-99	DRYNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	HOL0861538	62	Year(s)	Male Adult	22-Jun-99	(GENERALIZED)	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WIL0861836		Unknown	Female Adult	23-Jun-99	STINGING	US	N	SKIN	10	Day(s)
NOX ACNE PADS MAX 65 CT	BUR0862056	24	Year(s)	Female Adult	24-Jun-99	BURNING	US	N	SKIN	8	Hour(s)
NOX ACNE PADS MAX 90 CT	MUL0862584	14	Year(s)	Female Child	28-Jun-99	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	FAC0862895		Unknown	Female Adult	30-Jun-99	SCRATCH	US	N	SKIN	5	Hour(s)
NOX ASPTC ASTR REG 8 OZ	DEL0862880		Unknown	Female Adult	30-Jun-99	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	CHI0863028		Unknown	Unknown	01-Jul-99	BURNING	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	PAU0863336		Unknown	Female Adult	02-Jul-99	RASH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HAR0863414		Unknown	Female Adult	06-Jul-99	SCRATCH	US	N	INJURY	1	Hour(s)
NOX ACNE PADS MAX 65 CT	THO0863476	13	Year(s)	Male Child	06-Jul-99	RASH	US	N	SKIN	2	Week(s)
NOX ACNE PADS REG 65 CT	KEL0863438	22	Year(s)	Male Adult	06-Jul-99	SCRATCH	US	N	SKIN	4	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	WEL0863852		Unknown	Female Adult	07-Jul-99	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SUM0863804		Unknown	Female Adult	07-Jul-99	HIVES	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	QUI0864222		Unknown	Female Adult	09-Jul-99	IRRITATION	US	N	SKIN	3	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	JON0864326		Unknown	Female Adult	12-Jul-99	PEELING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	DAV0864371		Unknown	Female Adult	12-Jul-99	BURNING	US	N	EYE INDIRECT		
NOX ASPTC ASTR XTR 8 OZ	FIT0864497	31	Year(s)	Female Adult	12-Jul-99	BURNING	US	N	SKIN	5	Day(s)
NOX ASPTC ASTR XTR 8 OZ	DAN0864707	13	Year(s)	Female Adult	13-Jul-99	PIMPLES	US	N	SKIN	2	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	QUI0864599	25	Year(s)	Female Adult	13-Jul-99	PEELING	US	N	SKIN	3	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	DAN0865068	13	Year(s)	Female Child	15-Jul-99	BURNING	US	N	SKIN	1	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	RAM0866015		Unknown	Female Adult	21-Jul-99	STINGING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	SIM0866456	28	Year(s)	Female Adult	23-Jul-99	BUMPS	US	N	SKIN	2	Day(s)
NOX ASPTC ASTR XTR 8 OZ	HOP0866766	18	006	Male Child	26-Jul-99	NONE	US	N	INGESTION		
NOX ACNE PADS REG 65 CT	NAR0867137		Unknown	Male Adult	29-Jul-99	REDNESS	US	N	SKIN	10	Minute(s)
NOX ASPTC ASTR XTR 8 OZ	LAU0867257		Unknown	Female Adult	29-Jul-99	REDNESS	US	N	SKIN		Minute(s)
NOX ACNE PADS REG 90 CT	THO0867420		Unknown	Unknown	30-Jul-99	PIMPLES	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	TAC0867752	2	Year(s)	Male Child	02-Aug-99	NONE	US	N	INGESTION		
NOXZEMA PADS MAXIMUM STRENGTH ND	HOL0867704		Unknown	Female Adult	02-Aug-99	BURNING	US	N	SKIN		
NOX ORI PAD REG PAD NTNT 50 CT	WET0867998	15	Year(s)	Male Child	03-Aug-99	PIMPLES	CA	N	SKIN	1.5	Year(s)

NOX ACNE PADS MAX 65 CT	EWI0868977	13	Year(s)	Female Child	10-Aug-99	SCRATCH	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	VAN0869127	19	Year(s)	Female Adult	10-Aug-99	BUMPS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	BRO0869110		Unknown	Female Adult	10-Aug-99	ITCHING	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	NEW0869664	15	Year(s)	Female Child	13-Aug-99	SORES	US	Y	SKIN	2	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	CHI0869882		Unknown	Female Adult	16-Aug-99	STINGING	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	KES0870089		Unknown	Unknown	17-Aug-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	PAC0870396		Unknown	Female Adult	19-Aug-99	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	MCQ0871052	12	Year(s)	Female Child	24-Aug-99	ACNE	US	N	SKIN		Unknown
NOX ACNE PADS MAX 65 CT	WAS0871808	29	Year(s)	Female Adult	30-Aug-99	SCRATCH	CA	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	IVY0871934		Unknown	Female Adult	30-Aug-99	PIMPLES	US	N	SKIN	2	Month(s)
NOX ASPTC ASTR XTR 8 OZ	SMI0872367	26	Year(s)	Unknown	01-Sep-99	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	RUS0872464	11	Year(s)	Female Adult	02-Sep-99	IRRITATION	US	N	EYE	2	Day(s)
NOX ACNE PADS MAX 65 CT	TAY0872557		Unknown	Female Adult	02-Sep-99	ACNE	US	N	SKIN		Unknown
NOXZEMA PADS MAXIMUM STRENGTH ND	COR0872447		Unknown	Female Adult	02-Sep-99	PIMPLES	US	N	SKIN	1	Month(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	EPP0872741	20	Year(s)	Female Adult	03-Sep-99	DRYNESS	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	RON0872649		Unknown	Female Adult	03-Sep-99	STINGING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	TAY0872782		Unknown	Female Child	04-Sep-99	BURNING	US	N	INHALATION		
NOX ASPTC ASTR XTR 8 OZ	LOR0873279		Unknown	Unknown	08-Sep-99	REDNESS	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	RAY0873547	14	Year(s)	Female Child	09-Sep-99	REDNESS	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	STR0873716		Unknown	Male Adult	10-Sep-99	BUMPS	US	N	SKIN		
NOX ACNE PADS REG 65 CT	KIA0873731		Unknown	Female Adult	10-Sep-99	SCRATCH	US	N	SKIN	12	Hour(s)
NOX ASPTC ASTR REG 8 OZ	WIL0873640	80	Year(s)	Female Adult	10-Sep-99	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	MAG0873665		Unknown	Female Adult	10-Sep-99	RASH	US	N	SKIN	10	Day(s)
NOX ACNE PADS REG 90 CT	MC 0874200	14	Year(s)	Female Child	14-Sep-99	PIMPLES	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MC 0874214		Unknown	Female Adult	14-Sep-99	STINGING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HAG0874562		Unknown	Male Adult	16-Sep-99	PIMPLES	US	N	SKIN	2	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	UNK0874670	49	Year(s)	Female Adult	17-Sep-99	NONE	US	N	ORAL/NASAL		
NOXZEMA PADS MAXIMUM STRENGTH ND	CAR0874832		Unknown	Female Adult	20-Sep-99	DRYNESS	US	N	SKIN		Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	ELL0875389		Unknown	Female Adult	22-Sep-99	PIMPLES	US	N	SKIN	2	Week(s)
D-NOX PADS REG STR ND	SEG0875659		Unknown	Female Adult	23-Sep-99	BURNING	US	N	SKIN		
NOX ACNE PADS REG 65 CT	HEL0875910		Unknown	Female Adult	27-Sep-99	SHORT OF BREATH	US	N	INHALATION		
NOX ACNE PADS MAX 65 CT	DUN0876463		Unknown	Female Adult	29-Sep-99	IRRITATION	US	N	SKIN	10	Day(s)
NOX ACNE PADS REG 90 CT	WIL0876803		Unknown	Female Adult	01-Oct-99	PIMPLES	US	N	SKIN		Unknown
NOX ACNE PADS MAX 90 CT	ROB0877040	15	Year(s)	Female Adult	04-Oct-99	RASH	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	VAN0877175	19	Year(s)	Female Adult	04-Oct-99	PIMPLES	US	N	SKIN	30	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	ROB0877123	15	Year(s)	Female Adult	04-Oct-99	RASH	US	N	SKIN	10	Hour(s)
NOX ACNE PADS MAX 65 CT	PRE0877561		Unknown	Female Adult	06-Oct-99	BURNING	US	N	SKIN		

D-NOX PADS REG STR ND	FAL0877823		Unknown	Male Adult	07-Oct-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	NEW0878297		Unknown	Female Adult	11-Oct-99	REDNESS	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 65 CT	VAL0878277		Unknown	Female Adult	11-Oct-99	PEELING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	HEN0878438		Unknown	Female Adult	12-Oct-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	VID0878808	14	Year(s)	Female Child	14-Oct-99	RASH	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	VAL0878959	15	Year(s)	Female Child	15-Oct-99	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	FRA0878994	24	Year(s)	Female Adult	15-Oct-99	BURNING	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	MEA0879088		Unknown	Male Child	15-Oct-99	ACNE	US	N	SKIN	1	Week(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	BEN0879123		Unknown	Female Child	15-Oct-99	HIVES	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	YOU0880032		Unknown	Female Adult	22-Oct-99	SCRATCH	CA	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	ISO0880540		Unknown	Female Adult	26-Oct-99	DRYNESS	US	N	SKIN	6	Week(s)
NOX ACNE PADS MAX 65 CT	ZAG0880665		Unknown	Female Adult	27-Oct-99	DISCOLORATION	CA	N	SKIN	12	Hour(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	COO0881211	26	Year(s)	Male Adult	01-Nov-99	DIZZINESS	US	N	INGESTION	15	Minute(s)
D-NOX PADS REG STR ND	BOW0883217	53	Year(s)	Female Adult	12-Nov-99	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	DEI0883623		Unknown	Female Adult	15-Nov-99	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	POI0883597	32	Year(s)	Female Adult	15-Nov-99	SCRATCH	CA	N	SKIN		
NOX ACNE PADS MAX 90 CT	AMA0885348		Unknown	Female Adult	29-Nov-99	DRYNESS	US	N	SKIN		
D-NOX PADS REG STR ND	POT0885431		Unknown	Female Adult	30-Nov-99	DRYNESS	US	N	SKIN	1	Month(s)
NOX ACNE PADS MAX 90 CT	COR0885528	17	Year(s)	Male Child	30-Nov-99	PIMPLES	US	N	SKIN	2	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	LOR0885716		Unknown	Female Adult	01-Dec-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	LOR0885715	24	Year(s)	Female Adult	01-Dec-99	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	CLE0886046		Unknown	Female Adult	03-Dec-99	RASH	CA	N	SKIN	5	Day(s)
NOX ORI PAD MAX PAD NTNT 50 CT	HAM0887440	26	Year(s)	Female Adult	14-Dec-99	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	HAR0888412	15	Year(s)	Male Child	21-Dec-99	DRYNESS	US	N	SKIN		Unknown
NOX ASPTC ASTR REG 8 OZ	THO0888540		Unknown	Female Adult	22-Dec-99	RASH	US	N	SKIN	1	Day(s)
D-NOX PADS REG STR ND	GIO0888673		Unknown	Female Adult	27-Dec-99	DRYNESS	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	OWE0888941		Unknown	Female Adult	28-Dec-99	DRYNESS	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	SCA0889068		Unknown	Female Adult	28-Dec-99	SCRATCH	US	N	SKIN	9	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	CAR0889201		Unknown	Female Adult	29-Dec-99	REDNESS	US	N	SKIN	12	Hour(s)
NOX ASPTC ASTR XTR 8 OZ	WIL0889386	16	Year(s)	Female Child	30-Dec-99	BURNING	US	N	EYE		
NOX ASPTC ASTR XTR 8 OZ	SMI0889687	15	Year(s)	Female Child	04-Jan-00	DRYNESS	US	N	SKIN	2	Week(s)
NOX ORI PAD REG PAD NTNT 75 CT	STE0889493		Unknown	Female Adult	04-Jan-00	RASH	US	N	SKIN	5	Hour(s)
NOX ACNE PADS MAX 90 CT	WAR0890654	15	Year(s)	Male Child	10-Jan-00	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	ROD0891194	14	Year(s)	Male Child	13-Jan-00	PIMPLES	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 90 CT	ZYG0891773		Unknown	Female Adult	19-Jan-00	SCRATCH	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	DRA0891997		Unknown	Female Adult	20-Jan-00	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	RIC0891882	14	Year(s)	Female Child	20-Jan-00	SWELLING	US	N	SKIN	3	Day(s)

NOX ACNE PADS MAX 90 CT	CRE0892243	15	Year(s)	Female Child	24-Jan-00	REDNESS	US	N	SKIN	1	Day(s)
NOX ASPTC ASTR XTR 8 OZ	NEL0892320		Unknown	Female Adult	24-Jan-00	RASH	US	N	SKIN	1	Week(s)
NOX ACNE PADS MAX 65 CT	DEL0892636		Unknown	Female Adult	25-Jan-00	IRRITATION	US	N	SKIN	2	Week(s)
NOX ACNE PADS MAX 65 CT	BRI0892934	14	Year(s)	Female Child	26-Jan-00	PIMPLES	CA	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	HIL0893023		Unknown	Male Adult	27-Jan-00	SCRATCH	US	N	SKIN	8	Hour(s)
NOX ACNE PADS MAX 90 CT	LEG0893344		Unknown	Female Adult	28-Jan-00	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	RIC0893997	8	Year(s)	Male Child	02-Feb-00	HAIR LOSS (DIFFUSE)	US	N	SKIN		Unknown
NOXZEMA PADS MAXIMUM STRENGTH ND	FOR0894519		Unknown	Male Adult	04-Feb-00	BURNING	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	RAT0895474		Unknown	Male Adult	10-Feb-00	REDNESS	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	PUD0896102	38	Year(s)	Female Adult	15-Feb-00	RASH	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 65 CT	DUT0896466		Unknown	Female Adult	16-Feb-00	CUT, SCRATCH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SOT0897687	20	Year(s)	Female Adult	25-Feb-00	PIMPLES	US	N	SKIN	1	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	JEN0897883	23	Year(s)	Male Adult	28-Feb-00	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 90 CT	JOH0898001		Unknown	Female Adult	28-Feb-00	BURNING	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	GAM0898308		Unknown	Female Adult	01-Mar-00	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	CRU0901218		Unknown	Unknown	21-Mar-00	REDNESS	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	DAN0901859	14	Year(s)	Female Adult	24-Mar-00	STINGING	US	N	SKIN		
D-NOX PADS REG STR ND	MAZ0902142	40	Year(s)	Female Adult	27-Mar-00	RASH	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 65 CT	MOR0902357	14	Year(s)	Female Child	28-Mar-00	PIMPLES	CA	N	SKIN	3	Week(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	DEA0902625	28	Year(s)	Female Adult	30-Mar-00	REDNESS	US	N	SKIN	24	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	ILI0902589	35	Year(s)	Male Adult	30-Mar-00	DISCOLORATION	US	Y	SKIN	3	Year(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	BIA0902974		Unknown	Unknown	03-Apr-00	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	UNK0904289		Unknown	Unknown	11-Apr-00	RASH	CA	N	SKIN		
D-NOX PADS REG STR ND	SAN0904970		Unknown	Female Adult	17-Apr-00	BURNING	US	N	SKIN	2	Week(s)
NOX ASPTC ASTR XTR 8 OZ	REF0905184		Unknown	Male Adult	18-Apr-00	REDNESS	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WAH0905676		Unknown	Female Adult	24-Apr-00	REDNESS	US	N	SKIN	3	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	SHA0905718	26	Year(s)	Male Adult	24-Apr-00	DISCOLORATION	US	N	SKIN	14	Hour(s)
NOX ACNE PADS MAX 90 CT	MOR0906080	55	Year(s)	Female Adult	26-Apr-00	HIVES	US	N	SKIN	5	Day(s)
NOX ASPTC ASTR XTR 8 OZ	HUN0906455	23	Year(s)	Female Adult	27-Apr-00	BRUISE	US	N	SKIN	1	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	UNK0907594		Unknown	Unknown	05-May-00	NONE	US	N	INGESTION		
NOX ASPTC ASTR XTR 8 OZ	TOL0907548		Unknown	Female Adult	05-May-00	REDNESS	US	N	SKIN		
D-NOX PADS REG STR ND	MAD0909081	14	Year(s)	Female Adult	17-May-00	REDNESS	CA	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	FER0908989		Unknown	Female Adult	17-May-00	PIMPLES	US	N	SKIN	5	Day(s)
NOX ACNE PADS MAX 65 CT	KLI0909368	38	Year(s)	Female Adult	19-May-00	BLEEDING	US	N	SKIN	2	Day(s)
D-NOX PADS REG STR ND	MET0909975		Unknown	Female Adult	24-May-00	OTHER	US	N	SKIN	10	Month(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	GRO0909955	22	Year(s)	Female Adult	24-May-00	BURNING	US	N	SKIN		
D-NOX PADS REG STR ND	TRA0910138		Unknown	Female Adult	25-May-00	BURNING	US	N	SKIN		

NOX ACNE PADS MAX 90 CT	PER0910207		Unknown	Female Adult	25-May-00	BURNING	US	N	SKIN	6	Day(s)
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	UNK0910826	3	Year(s)	Unknown	31-May-00	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	SHI0911417	15	Year(s)	Female Adult	05-Jun-00	BRUISE	CA	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	TAY0912180		Unknown	Female Adult	12-Jun-00	ACNE	US	N	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	CAR0912464	13	Year(s)	Female Child	13-Jun-00	REDNESS	US	N	SKIN	2	Hour(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	LEE0912704	14	Unknown	Female Child	14-Jun-00	PEELING	CA	N	SKIN		
NOX ACNE PADS MAX 90 CT	SEA0913015	12	Year(s)	Female Adult	19-Jun-00	PIMPLES	US	N	SKIN		Unknown
NOX ACNE PADS REG 90 CT	FEH0913484	22	Year(s)	Female Adult	22-Jun-00	BURNING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	EAG0914679	18	006	Female Child	05-Jul-00	NONE	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	SPE0914674	30	Year(s)	Female Adult	05-Jul-00	SCRATCH	US	N	SKIN		
NOX ACNE PADS REG 90 CT	DAV0914894		Unknown	Unknown	06-Jul-00	BURNING	US	N	SKIN		
NOX ACNE PADS REG 90 CT	GOI0914895	35	Year(s)	Female Adult	06-Jul-00	IRRITATION	US	N	SKIN	2	Month(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	PRO0915979	29	Year(s)	Female Adult	18-Jul-00	PEELING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	TUC0916903	1	Year(s)	Female Child	26-Jul-00	VOMITING	US	N	INGESTION		
NOX ACNE PADS MAX 90 CT	AMA0917191			006	28-Jul-00	PIMPLES	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	LEM0917490	25	Year(s)	Female Adult	31-Jul-00	RASH	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	MC 0917423			006	31-Jul-00	BUMPS	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	PAT0917760	22	Year(s)	Female Adult	01-Aug-00	CUT	US	N	SKIN	1	Day(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	NIP0917767	29	Year(s)	Female Adult	01-Aug-00	SCRAPED	US	N	SKIN	1	Day(s)
NOX ACNE PADS MAX 90 CT	STR0917885	15	Year(s)	Female Child	02-Aug-00	ACNE	US	N	SKIN	4	Month(s)
NOX ACNE PADS MAX 65 CT	LAW0918154	14	Year(s)	Female Child	04-Aug-00	IRRITATION	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	SIG0918659			999	09-Aug-00	BURN	CA	N	SKIN		
NOX ACNE PADS MAX 65 CT	RAG0919360			006	16-Aug-00	BURNING	US	N	EYE INDIRECT		
NOX ACNE PADS MAX 90 CT	SHE0919399	30		006	16-Aug-00	BURN	US	N	SKIN		
NOX ACNE PADS MAX 90 CT	SCO0919794	14	Year(s)	Female Child	21-Aug-00	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	SPE0920155			006	22-Aug-00	BURNING	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	FAG0921166			006	30-Aug-00	REDNESS	CA	N	SKIN	1	Week(s)
NOX ASPTC ASTR XTR 8 OZ	DAW0922007	18		006	07-Sep-00	BURNING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	POT0924442			006	25-Sep-00	SCRATCH	US	Y	SKIN	2	Day(s)
NOX ACNE PADS MAX 90 CT	VIL0925778	33	Year(s)	Female Adult	03-Oct-00	BURN	US	N	SKIN	3	Day(s)
NOX ACNE PADS MAX 90 CT	FOW0926106			006	05-Oct-00	SCRATCH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	DOY0926359			006	06-Oct-00	PIMPLES	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	PRO0926429	12	Year(s)	Female Child	07-Oct-00	RASH	US	N	SKIN		
NOX ACNE PADS REG 65 CT	GOU0927121				12-Oct-00	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	BON0927307	2	Year(s)	Female Child	12-Oct-00	NONE	US	N	INGESTION		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	PRO0927749	23	006	Male Child	16-Oct-00	NONE	US	N	INGESTION		
NOX ACNE PADS REG 65 CT	HAL0928233			006	18-Oct-00	DISCOLORATION	US	N	SKIN		

NOX ACNE PADS MAX 90 CT	MOO0929410	21	Year(s)	Female Adult	26-Oct-00	ITCHING	US	N	SKIN		
DISC-NOXZEMA ASTRINGENT OILY SIZE ND	URL0930578	26	Year(s)	Female Adult	02-Nov-00	BAD TASTE IN MOUTH	US	N	INGESTION		
NOX ACNE PADS MAX 65 CT	COR0930618			006	02-Nov-00	RASH	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	KER0931102	23	Year(s)	Female Adult	06-Nov-00	DISCOLORATION	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	WAT0931943	23	Year(s)	Female Adult	09-Nov-00	PIMPLES	US	Y	SKIN		
NOX ACNE PADS REG 65 CT	WIL0932627			006	14-Nov-00	DRYNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	SIM0933496			006	21-Nov-00	PIMPLES	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	CHA0934083	46	Year(s)	Female Adult	27-Nov-00	REDNESS	CA	N	SKIN	1	Day(s)
NOX ACNE PADS REG 90 CT	HAR0934169	21	Year(s)	Male Adult	28-Nov-00	BURN	US	N	SKIN		
NOX ORI PAD MAX PAD NTNT 50 CT	SAN0934479		001	006	29-Nov-00	RASH	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	WRI0934924		001	006	04-Dec-00	PEELING	US	N	SKIN		
NOX ACNE PADS MAX 65 CT	KAN0935413	18	Year(s)	Female Adult	06-Dec-00	BURNING	CA	N	SKIN	3	Year(s)
NOXZEMA PADS MAXIMUM STRENGTH ND	SMI0935994		001	006	12-Dec-00	DRYNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	POS0936342		001	006	14-Dec-00	REDNESS	US	N	SKIN		
NOXZEMA PADS MAXIMUM STRENGTH ND	ROS0936407	20	Year(s)	Female Adult	14-Dec-00	PIMPLES	US	N	SKIN		
NOX ASPTC ASTR XTR 8 OZ	LOU0937348	20	Year(s)	Female Adult	21-Dec-00	BURNING	US	N	SKIN		

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CP 14

Clinical Study Report

CRA: Kathy Wiandt **Date:** June 12, 2001

Study Statistician: Jeanne Philippo **Retention Limit:** Until Superseded

Approved by: WZB 6/26/01

Subject: Results of Efficacy Evaluation of Two Handsoap Products and Two Towlette Products in a Modified Healthcare Personnel Handwash Study Versus *Escherichia coli* – CRB-01-05-066-HB / HT# 01-108592-11.

Objective:

The objective of this study was to determine the ability of four antibacterial products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments. Treatment comparisons were made between the two handwipe products and between the two handwash products.

Materials Tested:

Test Code	Test Material	Active Ingredient	Master Formula Number
A	Handwash Product	0% Salicylic Acid	SWH160-152
B	Handwash Product	2% Salicylic Acid	SWH160-155
C	Handwipe Product	1% Salicylic Acid	SWH94-136
D	Handwipe Product	0% Salicylic Acid	SWH94-137

Key Conclusions:

- All four treatments significantly reduced the level of *E. coli* on the hands after one product application versus baseline.
- All four treatments significantly reduced the level of *E. coli* on the hands after ten product applications versus baseline.
- After one wash, the 2.0% Salicylic acid handwash product had a significantly higher reduction in log counts versus the test placebo (p-value=0.001).
- After ten washes, the 2.0% Salicylic acid handwash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0001).
- After one wash, there was no significant difference between the 1.0% Salicylic acid handwipe and the placebo handwipe product.
- After ten washes, the 1.0% Salicylic acid handwipe had a significantly higher reduction in log counts versus the test placebo (p-value=0.0044).

The summary of the mean logs recovered and the log reductions achieved following the first and tenth washes were determined.

Table I –Summary of HCPHWT Log_{10} Bacterial Results								
		Baseline	**Log_{10}Counts – 1 Wash**			**Log_{10}Counts – 10 Washes**		
Treatment	Sample Size	Mean	Mean	Change from Baseline	% Reduction	Mean	Change from Baseline	% Reduction
A-Handsoap 0% Salicylic Acid	16	6.72	3.91	2.80	99.84	3.80	2.92	99.88
B-Handsoap 2% Salicylic Acid	16	6.81	3.52	3.29	99.95	3.00	3.80	99.98
C-Handwipe 1% Salicylic Acid	16	6.66	4.22	2.44	99.64	3.48	3.18	99.93
D-Handwipe 0% Salicylic Acid	16	6.63	4.34	2.30	99.49	4.19	2.44	99.64

Attached are tables containing the statistical summary of the study results.

Study Summary:

Test Site: Hill Top Research, Miamiville, Ohio

Study Dates: May 22 – June 6, 2001

Investigator: Gayle K. Mulberry, M.S.

Experimental Design: This was a randomized clinical study consisting of a four day test period and a follow-up visit. Four test products were evaluated. Sixteen subjects were used to evaluate each product. Each subject participated in a single test day and a follow-up visit.

Efficacy Measurements Taken: The subjects' hands were contaminated with a suspension of *Escherichia coli* ATCC 11229. Subjects' hands were contaminated eleven times and sampled three times using a plastic bag sampling procedure. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after one treatment with the assigned test product. After eleven contamination steps and ten treatments with the assigned test product the hands were sampled using the plastic bag sampling procedure.

Subject Demographics: Sixty-four (64) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions or creams and or antidandruff shampoos were enrolled into the study. Sixteen subjects were used to evaluate one of four test products.

Overview: To become familiar with the wash procedure using a liquid hand soap, the subjects assigned to the handwash products practiced the wash procedure with Baby-san®. To become familiar with the wipe procedure, subjects assigned to the handwipe products practiced the wipe procedure with Nice 'n' Clean®. For the base count, subjects' hands were contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands were removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands were contaminated with *E. coli*. After completing the contamination step, the subjects performed the test product application procedure with the assigned test product. For the subjects assigned to the hand wash products, the subjects lathered their hands for fifteen seconds and rinsed their hands for thirty seconds. For the subjects assigned to the handwipe product, the subjects wiped each hand for fifteen seconds. Approximately five minutes following the product treatment procedure, the organisms on both of the subjects' hands were removed using a plastic bag sampling procedure. Approximately five minutes following the tenth treatment, the organisms on the subjects' hands were removed using a plastic bag sampling procedure

Samples of the subjects' sampling solutions were diluted, plated, and incubated. Following incubation, the numbers of colony forming units (CFU's) were enumerated. Antibacterial activity was determined by comparing the number of bacteria removed from the hands after one treatment with the assigned test product and ten treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

Data Analysis:

The investigator was responsible for statistical analysis. For the bag juice results, each subject's base sampling CFU's was compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.05 were considered statistically significant. Percent change for each organism was computed by the following formula:

$$1 - \left(\frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}} \right) \times 100$$

Treatment comparisons were analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

Regulatory/Ethics Status:

This study was conducted in compliance with federal, state, and local regulations, guidelines, and standards including those related to Informed Consent and Good Clinical Practices as specified under 21 CRF 321.66. This study was conducted with IRB approval.

Subject Accountability:

Eighty subjects were screened for the study. Sixty-four subjects were screened, enrolled and completed this study. Sixteen subjects were excluded from the study.

Adverse Events:

There was one adverse event in this study. Subject #35 reported a head cold on 6/5/01. The adverse event was not related to the product treatment. The adverse event was resolved on 6/19/01.

Clinical Research Associate

Statistician

HTR Study Number 01-108592-11

Table 1A. CFU count summary statistics by HTR Code.

HTR Code	Sample Size	Base Count Mean	Base Count Median	Base Count Std. Error	Test Count 1 Mean	Test Count 1 Median	Test Count 1 Std. Error	Test Count 2 Mean	Test Count 2 Median	Test Count 2 Std. Error
HTR Code A	16	6.07E+06	6.25E+06	7.62E+05	1.26E+04	1.15E+04	2.63E+03	7.60E+03	5.92E+03	1.26E+03
HTR Code B	16	6.93E+06	7.35E+06	5.91E+05	4.19E+03	3.62E+03	5.49E+02	1.68E+03	1.38E+03	3.69E+02
HTR Code C	16	5.82E+06	6.46E+06	7.68E+05	3.76E+04	3.53E+04	9.42E+03	9.54E+03	4.84E+03	3.51E+03
HTR Code D	16	4.78E+06	4.31E+06	5.03E+05	3.73E+04	3.27E+04	6.87E+03	2.57E+04	1.76E+04	5.93E+03

Table 1B. Log10(Count) summary statistics by HTR Code.

HTR Code	Sample Size	Base Count Mean	Base Count Median	Base Count Std. Error	Test Count 1 Mean	Test Count 1 Median	Test Count 1 Std. Error	Test Count 2 Mean	Test Count 2 Median	Test Count 2 Std. Error
HTR Code A	16	6.7168	6.7957	0.0656	3.9120	4.0203	0.1128	3.7950	3.7580	0.0627
HTR Code B	16	6.8064	6.8648	0.0441	3.5155	3.5559	0.0950	3.0042	3.1257	0.1168
HTR Code C	16	6.6587	6.8059	0.0963	4.2173	4.5297	0.1944	3.4826	3.6610	0.2040
HTR Code D	16	6.6329	6.6197	0.0481	4.3366	4.4844	0.1433	4.1915	4.2367	0.1230

Table 1C. Log10 changes from baseline summary statistics and percent reductions.

HTR Code	Test Count 1 Sample Size	Test Count 1 Mean Change	Test Count 1 Median Change	Test Count 1 Std. Error Change	Test Count 1 Percent Reduction	Test Count 2 Sample Size	Test Count 2 Mean Change	Test Count 2 Median Change	Test Count 2 Std. Error Change	Test Count 2 Percent Reduction
HTR Code A	[illegible]	[illegible]	[illegible]	0.0651	[illegible]	16	[illegible]	2.9099	0.0647	99.88
HTR Code B	[illegible]	[illegible]	[illegible]	0.1011	[illegible]	16	3.8021	3.7333	0.1223	99.98
HTR Code C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16	[illegible]	3.1729	0.1628	99.93
HTR Code D	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16	[illegible]	[illegible]	0.1196	99.64

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code A	1	6.25E+06	6.00E+06	6.13E+06	1.96E+04	1.44E+04	1.70E+04	7.57E+03	7.52E+03	7.55E+03
	7	4.15E+06	4.40E+06	4.28E+06	5.26E+03	3.76E+03	4.51E+03	7.27E+03	4.30E+03	5.79E+03
	11	8.65E+06	9.50E+06	9.08E+06	2.14E+04	1.86E+04	2.00E+04	1.86E+04	1.15E+04	1.51E+04
	14	2.35E+06	2.18E+06	2.27E+06	2.09E+03	5.03E+03	3.56E+03	2.80E+03	6.69E+03	4.75E+03
	17	8.15E+06	5.55E+06	6.85E+06	1.93E+04	7.08E+03	1.32E+04	1.14E+04	9.80E+03	1.06E+04
	24	2.95E+06	3.85E+06	3.40E+06	8.50E+02	2.32E+03	1.59E+03	5.38E+03	3.19E+03	4.29E+03
	27	2.52E+06	2.25E+06	2.39E+06	1.15E+03	1.46E+03	1.31E+03	5.37E+03	3.03E+03	4.20E+03
	32	7.20E+06	9.30E+06	8.25E+06	9.00E+03	9.80E+03	9.40E+03	5.45E+03	2.93E+03	4.19E+03
	34	6.40E+06	6.35E+06	6.38E+06	6.46E+03	6.88E+03	6.67E+03	5.71E+03	4.38E+03	5.05E+03
	38	1.38E+07	1.16E+07	1.27E+07	4.60E+04	3.95E+04	4.28E+04	1.96E+04	2.48E+04	2.22E+04
	44	9.90E+06	9.20E+06	9.55E+06	2.45E+04	1.23E+04	1.84E+04	7.44E+03	1.40E+04	1.07E+04
	48	4.50E+06	6.15E+06	5.33E+06	5.49E+03	1.42E+04	9.85E+03	4.56E+03	7.55E+03	6.06E+03
	50	6.65E+06	9.35E+06	8.00E+06	2.07E+04	2.05E+04	2.06E+04	6.77E+03	8.85E+03	7.81E+03
	53	5.35E+06	3.30E+06	4.33E+06	1.56E+04	1.34E+04	1.45E+04	2.26E+03	2.96E+03	2.61E+03
	59	6.55E+06	7.25E+06	6.90E+06	1.58E+04	1.61E+04	1.60E+04	1.55E+03	5.84E+03	3.70E+03
	62	1.24E+06	1.45E+06	1.35E+06	1.61E+03	2.37E+03	1.99E+03	6.40E+03	7.65E+03	7.03E+03
HTR Code A		6.04E+06	6.11E+06	6.07E+06	1.34E+04	1.17E+04	1.26E+04	7.38E+03	7.81E+03	7.60E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code B	4	5.40E+06	4.10E+06	4.75E+06	6.38E+03	6.08E+03	6.23E+03	9.40E+02	1.87E+03	1.41E+03
	6	1.30E+07	1.14E+07	1.04E+07	9.40E+03	8.15E+03	8.78E+03	3.97E+03	3.75E+03	3.86E+03
	10	[illegible]	[illegible]	[illegible]	3.54E+03	4.14E+03	[illegible]	1.46E+03	1.24E+03	1.35E+03
	16	[illegible]	[illegible]	[illegible]	5.31E+03	1.45E+03	[illegible]	1.28E+03	1.60E+02	7.20E+02
	19	6.45E+06	9.05E+06	7.75E+06	1.99E+03	3.36E+03	2.68E+03	2.61E+03	2.06E+03	2.34E+03
	22	4.90E+06	7.25E+06	6.08E+06	7.20E+03	5.70E+03	6.45E+03	3.57E+03	5.94E+03	4.76E+03
	26	4.55E+06	5.10E+06	4.83E+06	2.45E+03	1.39E+03	1.92E+03	5.93E+03	3.02E+03	4.48E+03
	29	8.50E+06	9.60E+06	9.05E+06	1.80E+03	4.65E+03	3.23E+03	1.04E+03	4.10E+02	7.25E+02
	35	9.35E+06	9.20E+06	9.28E+06	2.12E+03	2.83E+03	2.48E+03	4.30E+02	1.80E+02	3.05E+02
	40	6.80E+06	8.35E+06	7.58E+06	5.07E+03	1.81E+03	3.44E+03	9.50E+02	2.21E+03	1.58E+03
	43	7.50E+06	9.80E+06	8.65E+06	3.89E+03	2.44E+03	3.17E+03	6.50E+02	2.30E+02	4.40E+02
	47	2.26E+06	3.30E+06	2.78E+06	4.72E+03	4.69E+03	4.71E+03	1.28E+03	4.20E+02	8.50E+02
	51	6.85E+06	7.40E+06	7.13E+06	3.11E+03	4.04E+03	3.58E+03	8.00E+01	1.60E+02	1.20E+02
	54	5.85E+06	5.35E+06	5.60E+06	4.06E+03	3.28E+03	3.67E+03	1.77E+03	1.92E+03	1.85E+03
	57	1.06E+07		1.06E+07	5.50E+03	9.75E+03	7.63E+03	1.24E+03	2.24E+03	1.74E+03
	64	3.65E+06	7.95E+06	5.80E+06	1.10E+02	3.20E+02	2.15E+02	1.80E+02	5.70E+02	3.75E+02
HTR Code B		6.34E+06	7.32E+06	6.93E+06	4.17E+03	4.21E+03	4.19E+03	1.71E+03	1.65E+03	1.68E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code C	2	3.04E+06	2.71E+06	2.88E+06	6.60E+03	1.24E+04	9.50E+03	3.69E+03	7.34E+03	5.52E+03
	5	6.10E+06	8.15E+06	7.13E+06	5.15E+04	6.70E+04	5.93E+04	2.12E+04	1.36E+04	1.74E+04
	9	8.70E+06	7.45E+06	8.08E+06	3.00E+04	7.95E+04	5.48E+04	3.03E+03	5.15E+03	4.09E+03
	13	2.58E+06	2.44E+06	2.51E+06	2.42E+03	3.00E+02	1.36E+03	1.96E+03	5.40E+02	1.25E+03
	18	3.60E+06	3.80E+06	3.70E+06	3.70E+04	2.42E+04	3.06E+04	8.20E+03	6.55E+03	7.38E+03
	23	2.70E+05	3.30E+05	3.00E+05	9.30E+02	2.00E+01	4.75E+02	4.00E+01	1.00E+02	7.00E+01
	25	7.60E+06	8.15E+06	7.88E+06	6.50E+04	2.70E+04	4.60E+04	5.95E+04	4.95E+04	5.45E+04
	31	5.70E+06	5.20E+06	5.45E+06	2.27E+04	1.33E+04	1.80E+04	7.70E+02	4.30E+02	6.00E+02
	33	2.37E+06	2.02E+06	2.20E+06	3.40E+04	5.15E+04	4.28E+04	4.80E+03	6.74E+03	5.77E+03
	39	5.85E+06	8.05E+06	6.95E+06	5.25E+04	2.70E+04	3.98E+04	5.80E+02	5.70E+02	5.75E+02
	41	5.25E+06	9.90E+06	7.58E+06	1.16E+04	5.66E+03	8.63E+03	3.11E+03	5.23E+03	4.17E+03
	46	8.55E+06	9.75E+06	9.15E+06	4.25E+04	7.70E+04	5.98E+04	1.21E+04	1.30E+04	1.26E+04
	52	3.00E+06	3.00E+06	3.00E+06	3.54E+03	3.61E+03	3.58E+03	1.70E+02	9.00E+01	1.30E+02
	55	6.40E+06	5.55E+06	5.98E+06	1.22E+05	1.90E+05	1.56E+05	2.67E+04	2.76E+04	2.72E+04
	58	8.75E+06	9.60E+06	9.18E+06	4.30E+04	3.24E+04	3.77E+04	3.50E+03	1.20E+03	2.35E+03
	61	1.24E+07	9.85E+06	1.11E+07	4.45E+04	2.12E+04	3.29E+04	1.10E+04	7.22E+03	9.11E+03
HTR Code C		5.64E+06	6.00E+06	5.82E+06	3.56E+04	3.95E+04	3.76E+04	1.00E+04	9.05E+03	9.54E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code D	3	[illegible]	2.20E+06	2.57E+06	1.02E+05	5.25E+04	7.73E+04	2.83E+03	2.38E+03	2.61E+03
	8	[illegible]	9.35E+06	8.05E+06	5.95E+04	9.05E+04	7.50E+04	9.70E+04	5.05E+04	7.38E+04
	12	[illegible]	3.27E+06	[illegible]	3.70E+04	2.78E+04	[illegible]	3.15E+04	3.70E+04	3.43E+04
	15	[illegible]	[illegible]	[illegible]	[illegible]	4.05E+04	[illegible]	[illegible]	2.75E+04	2.51E+04
	20	[illegible]	[illegible]	[illegible]	5.25E+04	[illegible]	[illegible]	[illegible]	2.22E+04	2.43E+04
	21	5.30E+06	6.50E+06	5.90E+06	5.15E+04	4.25E+04	4.70E+04	2.17E+04	1.82E+04	2.00E+04
	28	3.40E+06	3.05E+06	3.23E+06	1.46E+04	6.08E+03	1.03E+04	1.10E+04	1.00E+04	1.05E+04
	30	5.90E+06	6.10E+06	6.00E+06	4.25E+03	1.51E+04	9.68E+03	1.28E+04	1.75E+04	1.52E+04
	36	3.85E+06	3.65E+06	3.75E+06	2.53E+04	2.50E+04	2.52E+04	1.00E+04	9.05E+03	9.53E+03
	37	5.05E+06	7.15E+06	6.10E+06	4.30E+04	7.30E+04	5.80E+04	5.05E+04	6.70E+04	5.88E+04
	42	2.75E+06	3.38E+06	3.07E+06	6.59E+03	2.59E+03	4.59E+03	1.25E+03	1.44E+03	1.35E+03
	45	6.40E+06	8.20E+06	7.30E+06	3.90E+04	6.75E+04	5.33E+04	1.74E+04	1.20E+04	1.47E+04
	49	2.44E+06	3.50E+06	2.97E+06	1.16E+04	1.16E+04	1.16E+04	4.51E+03	7.29E+03	5.90E+03
	56	5.55E+06	3.80E+06	4.68E+06	1.20E+05	6.00E+04	9.00E+04	4.85E+04	2.35E+04	3.60E+04
	60	6.45E+06	6.75E+06	6.60E+06	5.35E+04	2.04E+04	3.70E+04	7.35E+03	6.34E+03	6.85E+03
	63	1.61E+06	2.21E+06	1.91E+06	1.20E+02	2.34E+03	1.23E+03	9.20E+04	5.35E+04	7.28E+04
HTR Code D		4.24E+06	5.32E+06	4.78E+06	4.01E+04	3.44E+04	3.73E+04	2.86E+04	2.28E+04	2.57E+04

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 1 Left Log10 CFU/ml	Test Count 1 Right Log10 CFU/ml	Test Count 1 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code A	1	4.2923	4.1584	4.2253	2.5617	
	7	3.7210	3.5752	3.6481	2.9827	
	11	4.3304	4.2695	4.3000	2.6574	
	14	3.3201	3.7016	3.5109	2.8439	
	17	4.2856	3.8500	4.0678	2.7599	
	24	2.9294	3.3655	3.1475	3.3802	
	27	3.0607	3.1644	3.1125	3.2643	
	32	3.9542	3.9912	3.9727	2.9402	
	34	3.8102	3.8376	3.8239	2.9806	
	38	4.6628	4.5966	4.6297	2.4725	
	44	4.3892	4.0899	4.2395	2.7402	
	48	3.7396	4.1523	3.9459	2.7751	
	50	4.3160	4.3118	4.3139	2.5830	
	53	4.1931	4.1271	4.1601	2.4633	
	59	4.1987	4.2068	4.2027	2.6355	
	62	3.2068	3.3747	3.2908	2.8366	0.0001*
HTR Code A		3.9006	3.9233	3.9120	2.8048	0.0001*

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 2 Left Log10 CFU/ml	Test Count 2 Right Log10 CFU/ml	Test Count 2 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code A	1	3.8791	3.8762	3.8777	2.9094	
	7	3.8615	3.6335	3.7475	2.8832	
	11	4.2695	4.0607	4.1651	2.7923	
	14	3.4472	3.8254	3.6363	2.7185	
	17	4.0569	3.9912	4.0241	2.8037	
	24	3.7308	3.5038	3.6173	2.9104	
	27	3.7300	3.4814	3.6057	2.7711	
	32	3.7364	3.4669	3.6016	3.3113	
	34	3.7566	3.6415	3.6991	3.1054	
	38	4.2923	4.3945	4.3434	2.7588	
	44	3.8716	4.1461	4.0089	2.9709	
	48	3.6590	3.8779	3.7685	2.9526	
	50	3.8306	3.9469	3.8888	3.0081	
	53	3.3541	3.4713	3.4127	3.2107	
	59	3.1903	3.7664	3.4784	3.3599	
	62	3.8062	3.8837	3.8449	2.2825	0.0001*
HTR Code A		3.7795	3.8105	3.7950	2.9218	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 1 Left Log10 CFU/ml	Test Count 1 Right Log10 CFU/ml	Test Count 1 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code B	4	3.8048	3.7839	3.7944	2.8782	
	6	3.9731	3.9112	3.9421	3.0706	
	10	3.5490	3.6474	3.5982	3.2812	
	16	3.7251	3.6464	3.6857	2.7840	
	19	3.2989	3.5263	3.4126	3.4705	
	22	3.8573	3.7559	3.8066	2.9687	
	26	3.3892	3.1430	3.2661	3.4167	
	29	3.2553	3.6675	3.4614	3.4945	
	35	3.3263	3.4518	3.3891	3.5782	
	40	3.7050	3.2577	3.4813	3.3958	
	43	3.5899	3.3874	3.4887	3.4445	
	47	3.6739	3.6712	3.6726	2.7638	
	51	3.4928	3.6064	3.5496	3.3029	
	54	3.6085	3.5159	3.5622	3.1856	
	57	3.7404	3.9890	3.8647	3.1606	
	64	2.0414	2.5051	2.2733	4.4581	0.0001*
HTR Code B		3.5019	3.5291	3.5155	3.2909	0.0001*

HTR Code	Subject	Test Count 2 Left Log10 CFU/ml	Test Count 2 Right Log10 CFU/ml	Test Count 2 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code B	4	2.9731	3.2718	3.1225	3.5501	
	6	3.5988	3.5740	3.5864	3.4263	
	10	3.1644	3.0934	3.1289	3.7505	
	16	3.1072	2.2041	2.6557	3.8141	
	19	3.4166	3.3139	3.3653	3.5179	
	22	3.5527	3.7738	3.6632	3.1120	
	26	3.7731	3.4800	3.6265	3.0563	
	29	3.0170	2.6128	2.8149	4.1409	
	35	2.6335	2.2553	2.4444	4.5229	
	40	2.9777	3.3444	3.1611	3.7160	
	43	2.8129	2.3617	2.5873	4.3458	
	47	3.1072	2.6232	2.8652	3.5711	
	51	1.9031	2.2041	2.0536	4.7989	
	54	3.2480	3.2833	3.2656	3.4821	
	57	3.0934	3.3502	3.2218	3.8035	
	64	2.2553	2.7559	2.5056	4.2258	0.0001*
HTR Code B		3.0396	2.9689	3.0042	3.8021	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

		Test Count 1				
HTR Code	Subject	Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code C	2	3.8195	4.0934	3.9565	2.5014	
	5	4.7118	4.8261	4.7689	2.0793	
	9	4.4771	4.9004	4.6887	2.2171	
	13	3.3838	2.4771	2.9305	3.4690	
	18	4.5682	4.3838	4.4760	2.0920	
	23	2.9685	1.3010	2.1348	3.3402	
	25	4.8129	4.4314	4.6221	2.2738	
	31	4.3560	4.1239	4.2399	2.4960	
	33	4.5315	4.7118	4.6216	1.7184	
	39	4.7202	4.4314	4.5758	2.2607	
	41	4.0645	3.7528	3.9086	2.9493	
	46	4.6284	4.8865	4.7574	2.2030	
	52	3.5490	3.5575	3.5533	2.9239	
	55	5.0864	5.2788	5.1826	1.5927	
	58	4.6335	4.5105	4.5720	2.3901	
	61	4.6484	4.3263	4.4873	2.5561	0.0001*
HTR Code C		4.3100	4.1245	4.2173	2.4414	0.0001*

		Test Count 2				
HTR Code	Subject	Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code		4.5670	3.8657	3.7161	2.7416	
	5	4.3263	4.1335	4.2299	2.6183	
	9	3.4814	3.7118	3.5966	3.3092	
	13	3.2923	2.7324	3.0123	3.3872	
	18	3.9138	3.8162	3.8650	2.7030	
	23	1.6021	2.0000	1.8010	3.6739	
	25	4.7745	4.6946	4.7346	2.1614	
	31	2.8865	2.6335	2.7600	3.9760	
	33	3.6812	3.8287	3.7550	2.5851	
	39	2.7634	2.7559	2.7597	4.0768	
	41	3.4928	3.7185	3.6056	3.2523	
	46	4.0828	4.1139	4.0984	2.8621	
	52	2.2304	1.9542	2.0923	4.3848	
	55	4.4265	4.4409	4.4337	2.3415	
	58	3.5441	3.0792	3.3116	3.6505	
	61	4.0414	3.8585	3.9500	3.0935	0.0001*
HTR Code C		3.5067	3.4586	3.4826	3.1761	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	--------Test Count 1-------- Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code D	3	5.0086	4.7202	4.8644	1.5410	
	8	4.7745	4.9566	4.8656	2.0345	
	12	4.5682	4.4440	4.5061	1.9224	
	15	4.3181	4.6075	4.4628	2.3777	
	20	4.7202	4.1335	4.4268	2.1505	
	21	4.7118	4.6284	4.6701	2.0985	
	28	4.1644	3.7839	3.9741	2.5338	
	30	3.6284	4.1790	3.9037	2.8744	
	36	4.4031	4.3979	4.4005	2.1733	
	37	4.6335	4.8633	4.7484	2.0304	
	42	3.8189	3.4133	3.6161	2.8680	
	45	4.5911	4.8293	4.7102	2.1498	
	49	4.0645	4.0645	4.0645	2.4013	
	56	5.0792	4.7782	4.9287	1.7334	
	60	4.7284	4.3096	4.5190	2.3004	
	63	2.0792	3.3692	2.7242	3.5514	0.0001*
HTR Code D		4.3307	4.3424	4.3366	2.2963	0.0001*

HTR Code	Subject	--------Test Count 2-------- Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code D	3	3.4518	3.3766	3.4142	2.9912	
	8	[illegible]	4.7033	4.8450	2.0550	
	[illegible]	[illegible]	[illegible]	4.5333	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	20	[illegible]	4.3464	4.3832	2.1942	
	21	4.3365	4.2601	4.2983	2.4703	
	28	4.0414	4.0000	4.0207	2.4872	
	30	4.1072	4.2430	4.1751	2.6030	
	36	4.0000	3.9566	3.9783	2.5956	
	37	4.7033	4.8261	4.7647	2.0141	
	42	3.0969	3.1584	3.1276	3.3565	
	45	4.2405	4.0792	4.1599	2.7001	
	49	3.6542	3.8627	3.7585	2.7073	
	56	4.6857	4.3711	4.5284	2.1336	
	60	3.8663	3.8021	3.8342	2.9852	
	63	4.9638	4.7284	4.8461	1.4295	0.0001*
HTR Code D		4.2129	4.1701	4.1915	2.4414	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 3. Results of the Wilcoxon-Mann-Whitney Test for the between treatment analysis of test articles.

Group	-Test Count 1-- p-value	-Test Count 2-- p-value
A vs B	0.0010*	0.0001*
C vs D	0.3080	0.0044*

* indicates significant difference between treatments

HTR Study No.: 01-108592-11
Sponsor Study No.: CRB-01-05-066-HB

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of Hill Top Research, Inc. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records.

Data reviewed by:

Thomas Asplan, A.A.S., B.S. — Date
Auditor, Quality Assurance

CLINICAL STUDY PROTOCOL

Clinical Research & Biometrics Department
Sharon Woods Technical Center
Cincinnati, Ohio 45241

Title:	Efficacy Evaluation Of Two Liquid Soap Products and Two Towelette Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*
Study Number:	CRB-01-05-066-HB / HT# 01-108592-11
Issue Date:	5/15/01
Products Tested:	Antibacterial Handsoap Prototype (2% Salicylic Acid) Control Handsoap Prototype (0% Salicylic Acid) Antibacterial Handwipe Prototype (1% Salicylic Acid) Control Handwipe Prototype (0% Salicylic Acid)
Test Facility:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Principal Investigator:	Gayle Mulberry, M.S.
Sub-Investigators:	Kathleen A. Baxter, B.S. Ann R. Brady, A.S.
Test Sponsor:	The Procter & Gamble Co., Inc. Sharon Woods Technical Center 11520 Reed Hartman Highway Cincinnati, Ohio 45241

		work	home
Sponsor Toxicologist:	Candace Doepker, Ph.D.	(513) 626-5536	
	Tim Long, Ph.D	(513) 626-4027	
Sponsor Representative/CRA:	Kathy Wiandt, B.A	(513) 626-5225	(513) 398-6035
Sponsor Statistician:	Jeanne Philippo, B.A.	(513) 626-5937	

Expected Study Start Date:	May 22, 2001
Expected Study End Date:	June 6, 2001

I. Study Objective and Background

A. Objective

The objective of the study is to determine the ability of four antibacterial products to significantly reduce transient microbial flora (*Escherichia coli* ATCC 11229) on the hands after a single treatment and after ten (10) treatments. Treatment comparisons will be made between the two handwipe products and between the two handwash treatments.

B. Background

The skin microflora can be divided into two (2) groups, the resident flora and the transient flora. The resident flora includes organisms that are consistently present on the skin. The transient flora are the contaminating skin organisms resulting from contact with the environment. They comprise a wide variety of Gram positive and Gram negative species that can be responsible for the spread of infections and gastrointestinal diseases.

Since the benefits that result from washing with antibacterial soaps can not be easily measured under consumer use conditions, it is necessary to do controlled clinical studies to demonstrate their efficacy. This clinical study is a modification of an ASTM test method, "Evaluation of Health Care Personnel Handwash Formulation"(1) and reported in the Tentative Final Monograph for Health Care Antiseptic Drug Products(2). It is used to determine the ability of an antimicrobial handwashing agent, when used in a hand washing procedure, to reduce the transient microbial flora (contaminants). This study is designed to demonstrate the efficacy of four antibacterial products in reducing the numbers of a marker organism, *Escherichia coli* ATCC 11229 on the hands after a contamination and a single handwash and after ten handwashes. Efficacy is determined by comparing the numbers of marker organisms on the hands before and after using the test products.

C. Study Safety Statement

This testing meets the ethical requirements stipulated in the Sponsor's Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

II. Study Summary

A. Overview

This randomized clinical study will consist of a four day test period and a follow-up visit. Four (4) test products will be evaluated. Sixty-four (64) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and or antidandruff shampoos (Appendix E), will be enrolled into the study. Sixteen (16) subjects will be used to evaluate each test product.

On the day of the study, the subjects will report to the clinical test facility. During this period, subjects' hands will be contaminated with a suspension of *E.coli*. Subjects' hands will be contaminated eleven (11) times and sampled three (3) times using a plastic bag sampling procedure. The first contamination and sampling will be for the determination of the base count. The second contamination and sampling will be for determination of the test count after one (1) treatment with the assigned Test Product. After eleven (11) contamination steps and ten (10) treatments with the assigned Test Products the hands will be sampled using the plastic bag sampling procedure

To become familiar with the wash procedure using the liquid hand soap, subjects assigned to handwash products will begin the test procedure by first performing a practice wash with Baby-san®. To become familiar with the wipe procedure using the towelette products, subjects assigned to handwipe products will begin the test procedure by first performing a practice wipe with Nice 'n' Clean®. For the base count, subjects will have their hands contaminated with *E. coli*. Immediately

following the contamination step, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands will be contaminated with *E. coli*. After completing the contamination step, the subjects will perform the test product application procedure with the assigned Test Product. Approximately five (5) minutes following the first procedure, the organisms on both of the subjects' hands will be removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Aliquots of the subjects' sampling solutions will be diluted, plated, and incubated. Following incubation, the number of colony forming units (CFU's) will be enumerated. Antibacterial activity is determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

B. Study Schedule

1. Subject Qualification and Enrollment

Prospective subjects will visit the test facility to be screened for their eligibility to participate in the study. Eligibility will be based upon information provided in the Demographics/Dermatological/ Medical History Form (DCF 1) and the Inclusion/Exclusion Form (DCF 2); and completion of a written informed consent (Appendix A).

2. Test Period

Subjects continuing on the study will be assigned a permanent subject number. Subjects will be assigned to one of the four test products according to the study randomization.

The following outlines the schedule of procedures for the test day:

1. Subjects will perform a practice wash with Baby-san® Handsoap or Nice "n' Clean® Handwipe(Appendix D).
2. Subjects will rinse their hands with 70% alcohol and rinse their hands under running tap water (Section G).
3. Subjects' hands will be contaminated (Section E).
4. Subjects' hands will be sampled for a base count (Section F).
5. Subjects will rinse their hands with water for 30 seconds (Section G).
6. Subjects will rinse their hands with 70% alcohol and rinse with tap water (Section G).
7. Subjects' hands will be contaminated (Section E).
8. Subjects will wash their hands following the wash procedure for the assigned Test Product (Section C, Appendix C).
9. Subjects' right and left hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds $\pm$ thirty (30) seconds after the first wash with the assigned Test Product (Section F).
10. The hands will be rinsed for thirty seconds.
11. Subjects will perform steps 7 and 8 (above) a total of nine (9) more times at a minimum of five (5) minutes between each wash procedure.
12. The subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds $\pm$ thirty (30) seconds after the tenth wash with the assigned Test Product (Section F).
13. Subjects' hands will be disinfected with a bland soap and water wash and Hibiclens® (4%

chlorhexidine gluconate) wash and with a 70% alcohol rinse (Section G).

Note: A detailed scheduled of the above procedures can be found in Appendix D.

To ensure that any delayed adverse events, such as primary skin infections, are reported to the Study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study Completion (Appendix B) before leaving the clinical site after they have completed the study. This sheet will instruct the subjects to examine their hands and wrists daily until the final scheduled visit for the presence of pimples, blisters, or raised, red itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection. Subjects, who notice such lesions, will be instructed to call the clinical test site. The subjects will return to the clinical test site within four (4) to nine (9) days after the study procedures have been completed to have their hands and wrists examined by a technician. The technician will complete DCF 3 for each subject on their follow-up visit.

C. Product Treatment Procedure

Subjects will wash their hands and wrists according to the procedure described in Product Treatment Procedure, Appendix C. In general the following should be noted:

- The temperature should be checked and recorded before each wash.
- The water pressure at each spigot to be used for the study should flow at 4 L/min.
- Subjects should remove all jewelry from hands and wrists prior to start of wash procedure.
- Water temperature should be maintained at 95 - 100° F.

D. Preparation of Bacterial Suspensions

A stock culture of *Escherichia coli*, ATCC 11229, will be prepared by transferring three (3) isolated colonies from an agar plate or slant aseptically to a tube containing sterile Trypticase Soy Broth (TSB). The inoculated broth will then be incubated for 24 ± 4 hours at 35 ± 2° C. At least three (3) additional 24 hour broth transfers will be made in tubes containing appropriate volumes TSB from this broth culture.

A 2-liter flask containing 1000 mL of TSB will be inoculated with 1.0 mL of the final 24 hour broth transfer. The flask will be incubated for 24 ± 4 hours at 35 ± 2° C. Prior to any withdrawal of culture, whether for hand contamination or for numbers assay, the suspension will be stirred or shaken. The suspension will be assayed for number of organisms at the beginning and end of the treatment period. A suspension will not be used for more than eight (8) hours.

E. Contamination

Note: Prior to contamination, subjects hands must be visibly dry. Also, care should be taken to ensure that the culture is evenly spread over both hands

A total volume of 4.5 mL of the assigned bacterial suspension will be dispensed into the subjects' cupped hands in 1.5 mL increments. After each 1.5 mL aliquot is added, the suspension will be rubbed thoroughly over the surface of both hands, not going above the wrist and avoiding the nail beds. Each application and spreading should last approximately twenty (20) seconds. Between each aliquot the hands will be held away from the body and allowed to air dry for approximately thirty (30) seconds. Following the third 1.5 mL aliquot, the hands are allowed to air dry for approximately one (1) minute. A record of base and test contaminations will be documented on Source Document 1 or 2.

F. Bacterial Sampling Procedure

For removal of bacteria from the subjects' hands, loose fitting plastic bags with low bioburden will be placed on each subject's right and left hands. A 75 mL aliquot of stripping solution [0.1% Triton X-100 in 0.075 M phosphate buffer, 1.0% polysorbate (Tween) 80, 0.3% Lecithin, pH 7.9] will be aseptically added into each bag. The same solution will be used for the base counts and test counts.

The bag on each hand will be secured at the wrist with a child's size tourniquet and massaged for one (1) minute in a uniform manner by a lab technician. Aliquots of the solution will be aseptically obtained directly from the bag without touching the hands in the process and will be appropriately diluted in a sterile diluent with the appropriate neutralizer within in one (1) minute of sampling. A record of base and test samplings will be documented on Source Document 1.

The solution samples for bacteria counts will be labeled by either an Investigator derived code or the actual subject's number so that the individuals who prepare the plates and count the CFU's are unaware of the sources of the sampling solution.

G. Disinfection of Hands

After the baseline sampling, the subjects will rinse their hands for thirty (30) seconds under running tap water. The subjects' hands will be disinfected with a 70% alcohol wash. Subjects' hands will be squirted with 70% alcohol for approximately ten (10) seconds. Subjects will rub the alcohol over the surface of their hands and wrists for approximately fifteen (15) seconds. Subjects will rinse their hands and wrists under running tap water for approximately fifteen (15) seconds and dry their hands and wrists with paper towels.

After the final sampling is completed, the subject's hands will be washed with a bland soap (provided by the investigator) for approximately for thirty (30) seconds and rinsed for approximately fifteen (15) seconds. The subjects' hands will then be washed with Hibiclens® (4% chlorhexidine gluconate) for at least sixty (60) seconds. Subjects' hands and wrists will be rinsed with a 70% alcohol wash for ten (10) seconds. The subjects will rub the alcohol on all surfaces of their hands for fifteen (15) seconds and allow their hands to air dry.

A record of each disinfection procedure will be recorded on Source Document 1.

H. Plating and Incubation of the Organisms

The *Escherichia coli* organisms in the sampling solution are to be counted using a standard surface inoculation technique.

Aliquots of dilutions of the base sampling solution from each sample bag representing dilutions of 10^{-4}, 10^{-5}, and 10^{-6} will be plated in duplicate.

Following the wash with the test product, a 1.0 mL aliquot of the previously diluted sampling solution from each sample bag will be plated onto three MacConkey's agar plates (approximately 0.33 mL per plate) to achieve a 10^{-1} dilution. Also, aliquots of dilutions of the sampling solution from each sample bag representing dilutions of 10^{-2}, 10^{-3}, 10^{-4} and 10^{-5} will be plated in duplicate. The MacConkey's agar plates will be incubated 18-24 hours at 35 ± 2°C. Standard plate counting procedures will be used to count the CFU's of *E. coli*. In general, the number of CFU's per sample will be determined by taking the average of the counts from the plates which are in the range of ≥ 25 to ≤ 250 CFU's. If there are no plates with counts within this range, the following rules will be used to determine which counts will be used for obtaining the number of CFU's for that specimen:

1. If all of the counts are below the prescribed range, the numbers below 25 from the undiluted plates will be used.

2. If the counts from the highest dilution are > 250, the numbers, obtained from using the estimated counting procedure described in Appendix F, will be used.

Results will be reported on DCF 4.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Data collection form (DCF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in DCF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or her designee.

A. Subject Inclusion Criteria

Subjects will be eligible for enrollment if they:

1. Are a male or female, over 18 years of age;
2. Have signed a written informed consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/Dermatological/ Medical History Form (DCF 1);
4. Have hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders;
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

Subjects will not be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of arm or hand wash study within the past 7 days;
3. Have cuts, lesions, or other skin disorders on their hands or wrists;
4. Have soap, detergent, antibiotic, and/or perfume allergies;
5. Have eczema or psoriasis on their hands or arms;
6. Are using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos in the home within the last week (Appendix E);
7. Have excessively long or artificial nails (≥2 mm free edge) which would interfere with sampling;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator, would preclude participation.

D. Subject Number Assignment and Randomization

Upon entry into the study, each subject will be assigned a screening number beginning with 1001. Subjects will be assigned a permanent consecutive number, beginning with 001, as they are accepted into the study. This number will be used to identify the subject for the duration of the study.

IV. Study Material

A. Test Product

The test products will be sent by the Sponsor to the clinical site prior to study initiation. The test products will be identified with the appropriate label affixed to the outside of each container.

B. Shipping of Treatment Products and Other Study Supplies

The quantity of all treatment products and other study supplies, shipped to and returned from the clinical site, will be documented by the test site. The treatment products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc." with the facility's full address and phone number);
3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator(s) will insure that all test products and study materials, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11520 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Kathy Wiandt

V. Other Study Documentation

A. Adverse Events

Should any unexpected or serious adverse event occur during the clinical study or as a result of test product or study procedures, the subject will be requested to return to the site to be examined by the investigator or designee. The Investigator will determine if the adverse event is likely to be associated with product treatment or the study procedures. The investigator or other qualified medical personnel will determine if the event warrants termination of participation and/or to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward L. Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Kathy Wiandt, 513-626-5225 (work) or 513-398-6035 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in DCF 5. If treatment by a physician is necessary, this treatment will be documented on DCF 6.

The following criteria will be used to determine the reporting time frame.

1. Any serious adverse events or adverse events requiring immediate medical attention will be reported to the Sponsor's Monitor immediately (night or day) by telephone.
2. Adverse events resulting in subject termination from the study will be reported during the immediate business day by telephone.
3. Adverse events that do not require discontinuation of test participation can be reported during the immediate business day or next business day by telephone.

4. In the event of a serious adverse reaction, not necessarily related to use of the test product, or in the event of a death from any cause, the Investigator must report the event to the Sponsor's Monitor and to the IRB as soon as possible..

B. Protocol Amendments

If it becomes necessary to modify this protocol, the modification will be documented by a protocol amendment signed by the investigator, a representative of the Sponsor and approved by the Institutional Review Board.. All amendments to the final protocol will be consecutively numbered and will describe any changes made and the rationale for making the changes.

C. Protocol Deviations

If a deviation from the final protocol occurs, it is the responsibility of the Investigator, or designee, to notify the Clinical Research Associate or designee. The Institutional Review Board will be notified within twenty-four hours of any deviation that poses additional risks to the subjects. The deviation and subsequent notification will be documented appropriately.

D. Study Monitoring

The Investigator will permit a representative of the Sponsor (usually the Clinical Research Associate) to visit the facility during the course of the study to monitor study progress. During the visit(s), the Investigator will permit the monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The study monitor will also be permitted to review and verify test articles, wash procedure, and any Investigator-generated or Sponsor-generated study documents. The monitor will document and discuss this visit with the Investigator, or his designee, including any problems that are to be resolved.

VI. Statistical Analyses

The investigator will be responsible for all statistical analyses. For the bag juice results, each subject's base sampling CFU's will be compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.05 will be considered statistically significant. Percent change for the test organism will be computed , if needed, by the following formula:

$$1 - \frac{\text{(geometric mean of the test CFU's)}}{\text{geometric mean of the baseline CFU's}} \times 100$$

Treatment comparisons will be made between the two wash treatments and the two wipe treatments. Treatment comparisons will be analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

VII. Investigator Responsibilities

A. Institutional Review Board (IRB) Review and Approval

Review by an IRB is required to conduct this study. A copy of the approval letter along with a list of the IRB members who acted on this protocol and a statement that the IRB is in compliance with current Good Clinical Practices (GCP) regulations will be provided to the Sponsor.

B. Subject Informed Consent

All subjects will be informed as to the type of study, the general nature of the products being tested, and any known or anticipated adverse reactions, which might result from participation. Each subject must provide the Investigator with written informed consent to serve as a participant in the study. Basic elements of informed consent are outlined in 21 CFR 50.25.

C. Final Report

The Sponsor will generate a final report of clinical results. The investigator will provide a detailed description of the adverse events and deviations from the protocol. The investigator will also include an accounting of the subjects screened, eliminated, enrolled and terminated. The Investigator will submit the legible copies of all data collection forms. The Sponsor may request one (1) copy of all data collection forms before the Investigator's report is ready for submission to the Sponsor.

D. Record Retention

The Investigator will retain all study records in accordance with the test facility's SOP's.

E. Confidentiality

The Investigator and employees of the test facility are obligated to keep any information confidential regarding any of the personal cleansing products and all aspects of the study, as subject to the terms and conditions of the Laboratory Services Agreement between the test facility and Sponsor.

VIII. References

1. *Annual Book of ASTM Standards*, Volume 11.04, ASTM Designation: E 1174-94, Standard Test Method for "Evaluation of Health Care Personnel Handwash Formulation".
2. Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule, 21 CFR Parts 333 and 369, *Federal Register*, Volume 59, No. 116, June 17, 1994.

IX. Attachments

The following Appendices, Data collection forms are included as attachments to the Final Protocol:

A	Written Informed Consent
B	Subject's Follow-up Instructions
C	Product Treatment
D	Schedule of Test Period Procedures
E	List of Representative Antibacterial/Antimicrobial Products
F	Microbiological Media and Methods

Data Collection Forms

1	Demographics/Dermatological/Medical History Form
2	Inclusion/Exclusion Form
3	Follow- up Visit
4	Microbiology Results
5	Adverse Event
6	Physician's Report Form

Source Documents

1	Treatment Phase (Baseline, Wash 1 and Wash 10)
2	Treatment Phase (Washes 2 through 9)

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Kathy Wiandt, B.A., Clinical Research Associate
Clinical Research and Biometrics Department

Date: 5/15/01

STATISTICIAN:

Jeanne C. Philippo,B.A., Statistician
Clinical Research and Biometrics Department

Date: 5/15/01

APPROVED BY:

Bruce Semple, M.D., Medical Director
Clinical Research and Biometrics Department

Date: 5/15/01

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Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator(s) for CRB-01-05-066-HB:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies including, but not limited to, those relating to Institutional Review Board (IRB), Informed Consent, and Good Clinical Practices.

I am aware that it is the responsibility of the Investigator to promptly report to the IRB all changes to the research activity and all unanticipated problems involving risk to human subjects. In addition, as Investigator, I am aware that a summary report must submitted to the IRB when the study is completed. These guidelines are in accordance with CFR 312.66. The Sponsor will be copied on all correspondence to and from the IRB.

Gayle K. Mulberry, M.S., Investigator — Date: 5-15-01

Kathleen A. Baxter, B.S., Sub-Investigator — Date: 5.15.01

Ann R. Brady, A.S., Sub-Investigator — Date: 5.15.01

Appendix A
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WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B
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SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Efficacy Evaluation Of Two Liquid Soap Products and Two Towelette Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia coli*". During this study, a quantity of bacteria (*E. coli)* was placed on the surface of both your hands. Although we do not expect you to have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your hands and wrists within four (4) to nine (9) days.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your hands and wrists daily. If you notice the appearance of any pimples, blisters or raised bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:00 am-5 p.m.) or at (513) 831-3354 after hours.

You are required to return to the test site for a follow-up visit. Your follow-up is scheduled for:

_____

Date Time

Thank you for your cooperation.

Appendix C

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PRODUCT TREATMENT PROCEDURE

Part I: *For subjects assigned to the Liquid Soap Product*

- **Water temperature should be maintained at 95 - 100° F.**
- **The temperature should be checked and recorded before each wash.**
- **The water pressure at each spigot to be used for the study should flow at 4 L/min.**
- **Subjects should remove all jewelry from hands and wrists prior to start of wash procedure.**

The following wash procedure will be performed by each subject:

1. Subjects will be instructed to wet their hands under the running water.
2. **2.0 mL of product** will be dispensed from a disposable syringe into the subjects' hands by a laboratory technician .
3. The technician will instruct the Subjects to lather all surfaces of their hands and wrists for **fifteen (15) seconds.**
4. Subjects will rinse their hands under running tap water for thirty (30) seconds.
5. A. For test washes #1 and #10, hands will not be dried.

   B. For test washes #2 through #9, subjects will dry their hands with paper towels.

   (Note: following the practice wash, subjects' hands will be disinfected and contaminated.)
6. Bags will be placed on the subjects' right and left hands for sampling after the first wash and after the tenth treatment. Sampling time will be approximately five (5) minutes following the wash with the test product.

OR

Part II: *For subjects assigned to the Towelette*

1. The technician will dispense the appropriate towelette test product into the subject's left hand using a gloved hand.
2. The subject will rub all surfaces of their right hand and wrist for fifteen (15) seconds while the technician instructs the subject to:
   - rub palm
   - rub back of hand
   - rub fingers and web areas between fingers
   - rub the tips of the fingers
3. The subject will transfer the wipe to their right hand.
4. The subject will rub their left hand and wrist for fifteen (15) seconds while the technician instructs the subjects to:
   - rub palm
   - rub back of hand
   - rub fingers and web areas between fingers
   - rub the tips of the fingers

Appendix D
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CRB-01-05-066-HB

SCHEDULE OF TEST PERIOD PROCEDURES

1. **Practice treatment with Test Product:**

   For subjects assigned to the Liquid Soap Products

   - subjects wet hands under running tap water
   - dispense 2.0 mL of Baby San® into subjects' hands
   - subjects lather hands and wrists for fifteen (15) seconds
   - subjects rinse hands under running tap water for thirty (30) seconds
   - subjects dry hands with a paper towel

   For subjects assigned to the Towelette Products

   - towelette is placed in subjects' left hand
   - subject will rub all surfaces of their right hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips
   - subject transfers towelette to right hand
   - subject will rub all surfaces of their left hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips

2. **70% alcohol rinse**
   - squirt backs and palms of subjects' hands with 70% alcohol for 10 seconds
   - subjects rub alcohol over hands for 15 seconds
   - subjects rinse hands under running tap water for 15 seconds
   - subjects dry hands with paper towels

3. **Base contamination**
   - dispense 1.5 mL aliquot of bacterial suspension onto both subjects' hands
   - subjects rub aliquot over hands for 20 seconds
   - allow subjects' hands to air dry for approximately 30 seconds
   - repeat application 2 times
   - allow subjects' hands to air dry 1 minute after the last application

4. **Base sampling**
   - place bags on subject's right and left hands
   - dispense 75 mL stripping solution into each bag
   - secure bags
   - massage for 1 minute
   - sample each bag

5. **Water rinse**
   - subjects rinse hands with water for 30 seconds

6. **70% alcohol rinse**
   - perform as above

7. **Test contamination (prior to Test Product treatments 1 through 10)**
   - perform as above under base contamination

8. **Test Products Treatments (treatments 1 through 10)**
   - perform as described under practice treatment
   - for treatments #1 and #10, hands will not be dried prior to sampling
   - for treatments # 2 through #9 subjects will dry hands with paper towels

9. **Test sampling - Following Treatment 1**
   - perform as above under base sampling
   - subjects rinse hands with water for 30 seconds after the first test sampling

10. **Test sampling - Following Treatment 10**
    - place bag on of the subject's hands
    - dispense 75 mL stripping solution into the bag
    - secure bag
    - massage for 1 minute
    - sample bag

11. **Disinfection**
    - subject rinse hands for thirty (30) seconds
    - squirt subjects' hands with 2 mL of bland soap
    - subjects wash hands and wrists for approximately 30 seconds
    - subjects rinse hands and wrists for approximately 15 seconds
    - squirt subjects' hands with 5 mL of Hibiclens®
    - subjects wash hands and wrists for at least 60 seconds
    - subjects rinse hands and wrists for 15 seconds
    - squirt backs, palms and wrists of subjects' hands with 70% alcohol for 10 seconds
    - subjects rub alcohol over hands and wrists for 15 seconds
    - subjects' hands will be allowed to air dry

Appendix E
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CRB-01-05-066-HB

LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Antibacterial Dishwashing Liquids

Dawn
Joy
Dial
Palmolive

Appendix F
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MICROBIOLOGICAL MEDIA AND METHODS

0.075M Phosphate Buffer Solution with Neutralizers

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80, 3 grams of lecithin, and 1.0 gram of Triton X-100. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ± 0.1 with 1 N HCl or 1 N NaOH. Dispense buffer in bottles so that after autoclaving the volume equals 75 ± 1 mL. Loosely cap bottles and sterilize in the autoclave at 121°C.

0.0375M Phosphate Buffer Solution with Neutralizers

Weigh 0.2 grams of KH_2PO_4, 5.05 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80 and 3 grams of lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ±0.1with 1 N HCl or 1 N NaOH. Dispense buffer in appropriate volumes. Loosely cap vessels and sterilize in the autoclave at
121°C.

MacConkey's Agar

Suspend 50 grams in 1 liter of distilled or deionized water. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45-50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Data Collection Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-IIB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male ☐ Female	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER	No	Yes	Don't Know
1. Psoriasis ?			
2. Eczema ?			
3. Skin Cancer ?			
4. Skin Allergies ? Please specify:			
5. Hives ?			

Does the Subject have any of the following (present and past)?

II. OTHER MEDICAL INFORMATION	No	Yes	Don't Know
1. Allergies.? Please specify.			
2. Hepatitis ?			
3. Heart and Vascular Disease?			
4. Liver Disease ?			
5. Kidney Disease ?			
6. Tuberculosis ?			
7. Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8. Cancer ?			
9. Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10. Organ transplant ?			
11. Any other condition not listed ? Please specify:			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION	No	Yes	Don't Know
1. Antibiotics, oral or systemic ?			
2. Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3. Heart Medication ?			
4. Insulin ?			
5. Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: _____/_____/_____ mm dd yy

Data Collection Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA

Check one YES	NO	Subject:
		1. Is ≥ 18 years ?
		2. Has signed informed consent?
		3. Is healthy as evidenced by responses on DCF 1 ?
		4. Has hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA

YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility ?
			2. Has participated in any type of hand or arm wash study within the past 7 days ?
			3. Has cuts, lesions, or other skin disorders on their hands or wrists ?
			4. Has soap, detergent, antibiotic and/or perfume allergies ?
			5. Has eczema or psoriasis on their hands or wrists ?
			6. Has used antibacterial/antimicrobial soaps, medicated lotions and creams and/or anti-dandruff shampoos within the last week?
			7. Has long (≥ 2 mm free edge) or artificial nails
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Data Collection 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Interviewer's Signature	Date: ___/___/___ mm dd yy
Investigator's Signature::	Date: ___/___/___ mm dd yy

Data Collection Form 3

FOLLOW-UP VISIT

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB		Follow-up	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date Subject Entered the Study:	Follow-up Visit Date :
___/___/___ mm dd yy	___/___/___ mm dd yy

Does the subject's hands have the presence of pimples, blisters, or raised itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection ?

YES NO If yes, complete below:

Clinical Observations: (Include date of onset and descriptions severity locations, etc.)

_____

_____

Comments: _____

_____

_____

_____

_____

_____

Has the subject had any health related issues since the treatment procedure?

YES NO If yes, complete below:

Comments: _____

_____

_____

_____

_____

_____

Investigator's Signature or designee	Date ___/___/___ mm dd yy

Data Collection Form 4
MICROBIOLOGICAL RESULTS

Study #	Hill Top Research, Inc.	Subject Intials	Permanent #
01-108592-11 CRB 01-04-051-HB		___/___/___ F M L	

BASE - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS			RIGHT HAND DILUTIONS		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
1						
2						

TEST #1 (after first treatment) - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS					RIGHT HAND DILUTIONS				
	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}
1										
2										
3										

TEST #2 (after tenth treatment) - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS					RIGHT HAND DILUTIONS				
	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}
1										
2										
3										

Base Microbiologist(s):	**Date:**
Test Microbiologist(s):	**Date:**

*10^{-1} = 1 mL of sampling solution spread across three plates.

Data Collection Form 5

ADVERSE EVENT

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB			___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician

☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm dd yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
			/ /	
			/ /	
			/ /	

Investigator's Signature:	Recorded by:	Date ___/___/___ mm dd yy

Data Collection Form 6

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB			___ ___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature _____ Date

Source Document 1
TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108592-11 CRB-01-05-066-HB			

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Practice Wash	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	
Base Contamination Procedure	am/pm	☐ Yes / ☐ No	
Base Bacterial Sampling Procedure	am/pm	☐ Yes / ☐ No	
Base Decontamination	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #1	am/pm	☐ Yes / ☐ No	
Test Product Treatment #1	am/pm	☐ Yes ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #1 (after first treatment)	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #10	am/pm	☐ Yes / ☐ No	
Test Product Treatment #10	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #2 (after 10th treatment)	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	**Water Temp:** °F

Recorder's Signature:	Date: _____/_____/_____
Reviewer's Signature:	Date: _____/_____/_____

TREATMENT PHASE

Study #	Hill Top Research, Inc.	Permanent #'s
01-108592-11 CRB-01-05-066-HB		

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Test Contamination Procedure #2	am/pm	☐ Yes / ☐ No	
Test Product Treatment #2	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #3	am/pm	☐ Yes / ☐ No	
Test Product Treatment #3	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #4	am/pm	☐ Yes / ☐ No	
Test Product Treatment #4	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #5	am pm	☐ Yes / ☐ No	
Test Product Treatment #5	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #6	am/pm	☐ Yes / ☐ No	
Test Product Treatment #6	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #7	am/pm	☐ Yes / ☐ No	
Test Product Treatment #7	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #8	am/pm	☐ Yes / ☐ No	
Recorder's Signature:		Date: _____/_____/_____	
Reviewer's Signature:		Date: _____/_____/_____	

Source Document 2 (*continued*)
TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108592-11 CRB-01-05-066-HB			

Test Product Treatment #8	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #9	am/pm	☐ Yes / ☐ No	
Test Product Treatment #9	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Recorder's Signature:		Date: ____/____/____	
Reviewer's Signature:		Date: ____/____/____	

PILOT STUDY

RINSE OFF FORMULATION

SWH094-152, SW094-155

Clinical Study Report

CRA: Kathy Wiandt **Date:** May 23, 2001

Study Statistician: Jeanne Philippo **Retention Limit:** Until Superseded

Approved by: PBi 5/30/01

Subject: Results of Efficacy Evaluation of Two Handsoap Products in a Modified Healthcare Personnel Handwash Study Versus *Escherichia coli* – CRB-01-05-065-HB / HT# 01-108591-11.

Objective:

The objective of this study was to determine the ability of two antibacterial handsoap products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

Materials Tested: mf

Test Code	Test Material	Active Ingredient	Batch Number
A	Handwash Product	0% Salicylic Acid	SWH160-152
B	Handwash Product	2% Salicylic Acid	SWH160-155

Key Conclusions:

- After 1 wash, the 2.0% SA Hand Wash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0043).
- After 10 washes, the 2.0% SA Hand Wash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0022).

The summary of the mean logs recovered and the log reductions achieved following the first and tenth washes were determined.

Table I –Summary of HCPHWT Log_{10} Bacterial Results

		Baseline	Log_{10}Counts – 1 Wash			Log_{10}Counts – 10 Washes		
Treatment	Sample Size	Mean	Mean	Change from Baseline	% Reduction	Mean	Change from Baseline	% Reduction
A-Handsoap 0% Salicylic Acid	6	7.63	5.21	2.42	99.6	5.44	2.19	99.4
B-Handsoap 2% Salicylic Acid	6	7.74	4.66	3.09	99.9	4.53	3.21	99.9

Study Summary:

Test Site: Hill Top Research, Miamiville, Ohio

Study Dates: May 8-14, 2001

Investigator: Gayle K. Mulberry, M.S.

Experimental Design: This was a randomized clinical study consisting of a one day test period and a single follow-up visit. Two test products were evaluated. Six subjects were used to evaluate each product.

Efficacy Measurements Taken: The subjects' hands were contaminated with a suspension of *E.coli*. Subjects' hands were contaminated eleven times and sampled three times using a plastic bag sampling procedure. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after one treatment with the assigned Test Product. After eleven contamination steps and ten treatments with the assigned Test Products the hands were sampled using the plastic bag sampling procedure.

Subject Demographics: Twelve male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions or creams and or antidandruff shampoos were enrolled into the study. Six subjects were used to evaluate one of two test products.

Overview: To become familiar with the wash procedure using a liquid hand soap, the subjects practiced the wipe procedure with Baby-san®. For the base count, subjects' hands were contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands were removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands were contaminated with *E. coli*. After completing the contamination step, the subjects performed the test product application procedure with the assigned Test Product. The subjects lathered their hands for fifteen seconds and rinsed their hands for thirty seconds. Approximately five minutes following the wipe procedure, the organisms on both of the subjects' hands were removed using a plastic bag sampling procedure. Approximately five minutes following the tenth treatment, the organisms on the subjects' hands were removed using a plastic bag sampling procedure

Samples of the subjects' sampling solutions were diluted, plated, and incubated. Following incubation, the numbers of colony forming units (CFU's) were enumerated. Antibacterial activity was determined by comparing the number of bacteria removed from the hands after one treatment with the assigned Test Product and ten treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

Data Analysis:

For the bag juice results, each subject's base sampling CFU's was compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 were considered statistically significant. Percent change for each organism was computed by the following formula:

$$1 - \left(\frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}}\right) \times 100$$

Treatment comparisons were analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

Regulatory/Ethics Status:

This study was conducted in compliance with federal, state, and local regulations, guidelines, and standards including those related to Informed Consent and Good Clinical Practices as specified under 21 CRF 321.66.

Subject Accountability:

Twenty subjects were screened for the study. Twelve (12) subjects were screened, enrolled and completed this study. Five subjects met the study qualifications, but were excluded because they were extra subjects.

Two subjects were excluded because of open cuts on their hands. One subject was excluded because they were allergic to penicillin.

Adverse Events:

There were no adverse events in this study.

K Marriott
Clinical Research Associate

Jeanne C. Philippo
Statistician

HTR Study No.: 01-108591-11
Sponsor Study No.: CRB-01-05-065-HB

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of Hill Top Research, Inc. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records.

Data reviewed by:

Thomas Asplan 5-17-01

Thomas Asplan, A.A.S, B.S. Date
Auditor, Quality Assurance

CLINICAL STUDY PROTOCOL

Clinical Research & Biometrics Department
Sharon Woods Technical Center
Cincinnati, Ohio 45241

Title:	Efficacy Evaluation Of Two Liquid Soap Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*
Study Number:	CRB-01-05-065-HB HT# 01-108591-11
Issue Date:	5/4/01
Products Tested:	Antibacterial Handsoap Prototype Antibacterial Handsoap Prototype
Test Facility:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Microbiology Samples	The Procter and Gamble Company Miami Valley Laboratories
Principal Investigator:	Gayle Mulberry, M.S.
Sub-Investigators:	Kathleen A. Baxter, B.S. Ann R. Brady, A.S.
Test Sponsor:	The Procter & Gamble Co., Inc. Sharon Woods Technical Center 11520 Reed Hartman Highway Cincinnati, Ohio 45241

		work	home
Sponsor Toxicologist:	Candace Doepker, Ph.D	(513) 626-5536	
Sponsor Representative/CRA:	Kathy Wiandt, B.A.	(513) 626-5225	(513) 398-6035
Sponsor Statistician:	Jeanne Philippo, B.A.	(513) 626-5937	

Expected Study Start Date: May 8, 2001

Expected Study End Date: May 14, 2001

I. Study Objective and Background

A. Objective

The objective of the study is to determine the ability of a two antibacterial handwash product containing to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

B. Background

The skin microflora can be divided into two (2) groups, the resident flora and the transient flora. The resident flora includes organisms that are consistently present on the skin. The transient flora are the contaminating skin organisms resulting from contact with the environment. They comprise a wide variety of Gram positive and Gram negative species that can be responsible for the spread of infections and gastrointestinal diseases.

Since the benefits that result from washing with antibacterial soaps can not be easily measured under consumer use conditions, it is necessary to do controlled clinical studies to demonstrate their efficacy. This clinical study is a modification of an ASTM test method, "Evaluation of Health Care Personnel Handwash Formulation"(1) and reported in the Tentative Final Monograph for Health Care Antiseptic Drug Products(2). It is used to determine the ability of an antimicrobial handwashing agent, when used in a hand washing procedure, to reduce the transient microbial flora (contaminants). This study is designed to demonstrate the efficacy of two liquid handsoaps in reducing the numbers of a marker organism, *Escherichia coli* ATCC 11229 on the hands after a contamination and a single handwash and after ten handwashes. Efficacy is determined by comparing the numbers of marker organisms on the hands before and after using the test products.

C. Study Safety Statement

This testing meets the ethical requirements stipulated in the Sponsor's Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

II. Study Summary

A. Overview

This randomized clinical study will consist of a one day test period and a follow-up visit. Two (2) test products will be evaluated. Twelve (12) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and or antidandruff shampoos (Appendix E), will be enrolled into the study. Six (6) subjects will be used to evaluate each test product.

On the day of the study, the subjects will report to the clinical test facility. During this period, subjects' hands will be contaminated with a suspension of *E.coli*. Subjects' hands will be contaminated eleven (11) times and sampled three (3) times using a plastic bag sampling procedure. The first contamination and sampling will be for the determination of the base count. The second contamination and sampling will be for determination of the test count after one (1) treatment with the assigned Test Product. After eleven (11) contamination steps and ten (10) treatments with the assigned Test Products the hands will be sampled using the plastic bag sampling procedure

To become familiar with the wash procedure using the liquid hand soap, the subjects will begin the test procedure by first performing a practice wash with Baby-san®. For the base count, subjects will have their hands contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands will be contaminated with *E. coli*. After completing the contamination step, the subjects will perform the test product application procedure with the assigned

Test Product. Approximately five (5) minutes following the first procedure, the organisms on both of the subjects' hands will be removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure

Aliquots of the subjects' sampling solutions will be diluted, plated, and incubated. Following incubation, the number of colony forming units (CFU's) will be enumerated. Antibacterial activity is determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

B. Study Schedule

1. Subject Qualification and Enrollment

Prospective subjects will visit the test facility to be screened for their eligibility to participate in the study. Eligibility will be based upon information provided in the Demographics/Dermatological/ Medical History Form (DCF 1) and the Inclusion Exclusion Form (DCF 2); and completion of a written informed consent (Appendix A).

2. Test Period

Subjects continuing on the study will be assigned a permanent subject number. Subjects will be assigned to one of the two test products according to the study randomization.

The following outlines the schedule of procedures for the test day:

1. Subjects will perform a practice wash with Baby-san® (Appendix D).
2. Subjects will rinse their hands with 70% alcohol and rinse their hands under running tap water (Section G).
3. Subjects' hands will be contaminated (Section E).
4. Subjects' hands will be sampled for a base count (Section F).
5. Subjects will rinse their hands with water for 30 seconds (Section G).
6. Subjects will rinse their hands with 70% alcohol and rinse with tap water (Section G).
7. Subjects' hands will be contaminated (Section E).
8. Subjects will wash their hands following the wash procedure for the assigned Test Product (Section C, Appendix C).
9. Subjects' right and left hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the first wash with the assigned Test Product (Section F).
10. The hands will be rinsed for thirty seconds.
11. Subjects will perform steps 7 and 8 (above) a total of nine (9) more times at a minimum of five (5) minutes between each wash procedure.
12. The subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the tenth wash with the assigned Test Product (Section F).
13. Subjects' hands will be disinfected with a bland soap and water wash and Hibiclens® (4% chlorhexidine gluconate) wash and with a 70% alcohol rinse (Section G).

Note: A detailed scheduled of the above procedures can be found in Appendix D.

To ensure that any delayed adverse events, such as primary skin infections, are reported to the Study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study

Completion (Appendix B) before leaving the clinical site after they have completed the study. This sheet will instruct the subjects to examine their hands and wrists daily until the final scheduled visit for the presence of pimples, blisters, or raised, red itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection. Subjects, who notice such lesions, will be instructed to call the clinical test site. The subjects will return to the clinical test site within four (4) to nine (9) days after the study procedures have been completed to have their hands and wrists examined by a technician. The technician will complete DCF 3 for each subject on their follow-up visit.

C. Product Treatment Procedure

Subjects will wash their hands and wrists according to the procedure described in Product Treatment Procedure, Appendix C. In general the following should be noted:

a. Water temperature should be closely monitored and maintained at 95-100°F. The water temperature should be recorded on Source Document 1 or 2 before each wash.
b. Water pressure should be adjusted to a flow of 4 L/minute. This may be accomplished by placing a 2000 mL glass beaker or flask under each spigot to be used for subjects' hand washing. Allow the water to flow into the beaker. Adjust the water flow at each spigot accordingly, so that the beaker fills within thirty (30) seconds.
c. Subjects are to be closely supervised as they lather and wash their hands and wrists. The washes will be recorded on Source Documents 1 or 2.

D. Preparation of Bacterial Suspensions

A stock culture of *Escherichia coli*, ATCC 11229, will be prepared by transferring at least isolated (3) colony from an agar plate or slant aseptically to a tube containing sterile Trypticase Soy Broth (TSB). The inoculated broth will then be incubated for 24 ± 4 hours at 35 ± 2° C. At least three (3) additional 24 hour broth transfers will be made in tubes containing appropriate volumes TSB from this broth culture.

A 2-liter flask containing 1000 mL of TSB will be inoculated with 1.0 mL of the final 24 hour broth transfer. The flask will be incubated for 24 ± 4 hours at 35 ± 2° C. Prior to any withdrawal of culture, whether for hand contamination or for numbers assay, the suspension will be stirred or shaken. The suspension will be assayed for number of organisms at the beginning and end of the treatment period. A suspension will not be used for more than eight (8) hours.

E. Contamination

Note: Prior to contamination, subjects hands must be visibly dry. Also, care should be taken to ensure that the culture is evenly spread over both hands.

A total volume of 4.5 mL of the assigned bacterial suspension will be dispensed into the subjects' cupped hands in 1.5 mL increments. After each 1.5 mL aliquot is added, the suspension will be rubbed thoroughly over the surface of both hands, not going above the wrist and avoiding the nail beds. Each application and spreading should last approximately twenty (20) seconds. Between each aliquot the hands will be held away from the body and allowed to air dry for approximately thirty (30) seconds. Following the third 1.5 mL aliquot, the hands are allowed to air dry for approximately one (1) minute. A record of base and test contaminations will be documented on Source Document 1 or 2.

F. Bacterial Sampling Procedure

For removal of bacteria from the subjects' hands, loose fitting plastic bags with low bioburden will be placed on each subject's right and or left hands. A 75 mL aliquot of stripping solution [0.1% Triton X-100 in 0.075 M phosphate buffer, 1.0% polysorbate (Tween) 80, 0.3 % Lecithin, pH 7.9] will be aseptically added into each bag. The same solution will be used for the base counts and test counts.

The bag on each hand will be secured at the wrist with a child's size tourniquet and massaged for one (1) minute in a uniform manner by a lab technician. Aliquots of the solution will be aseptically obtained directly from the bag without touching the hands in the process and will be appropriately diluted in a sterile diluent with the appropriate neutralizer (for the test wash samples only). A record of base and test samplings will be documented on Source Document 1.

The solution samples for bacteria counts will be labeled by either an Investigator derived code or the actual subject's number so that the individuals who prepare the plates and count the CFU's are unaware of the sources of the sampling solution.

The solution will be aseptically placed in a sterile test tube. The test tube will be affixed with the subject number, baseline or post-treatment, and placed on ice for microbiological analysis. The sponsor will analyze the samples for microbiological content. The transfer of the microbial specimens will be recorded on Source Document 3.

G. Disinfection of Hands

After the baseline sampling, the subjects will rinse their hands for thirty (30) seconds under running tap water. The subjects' hands will be disinfected with a 70% alcohol wash. Subjects' hands will be squirted with 70% alcohol for approximately ten (10) seconds. Subjects will rub the alcohol over the surface of their hands and wrists for approximately fifteen (15) seconds. Subjects will rinse their hands and wrists under running tap water for approximately fifteen (15) seconds and dry their hands and wrists with paper towels.

After the final sampling is completed, the subject's hands will be washed with a bland soap (provided by the investigator) for approximately for thirty (30) seconds and rinsed for approximately fifteen (15) seconds. The subjects' hand will then be washed with Hibiclens® (4% chlorhexidine gluconate) for at least sixty (60) seconds. Subjects' hands and wrists will be rinsed with a 70% alcohol wash for ten (10) seconds. The subjects will rub the alcohol on all surfaces of their hands for fifteen (15) seconds and allow their hands to air dry.

A record of each disinfection procedure will be recorded on Source Document 1.

H. Plating and Incubation of the Organisms

Baseline specimens will be serially diluted in half-strength (0.0375 M) buffer (without Trtion X-100) in ten-fold dilutions to 10^{-3}, 10^{-4} and 10^{-5}. The diluted specimens will be plated using an automated plating system (Eddyjet system) onto MacConkey's agar. Post treatment specimens will be serially diluted in ten-fold dilutions to 10^{-1}, 10^{-2} 10^{-3} and 10^{-4}. Using an automated plating system (Eddyjet system), the undiluted and diluted specimens will be plated onto MacConkey's agar. The media for these analyses are shown in Appendix F.

Plated samples will be incubated aerobically for 18 - 24 hours at 35 $\pm$ 2°C. The plates will be analyzed using the Countermat®. The results will be reported as colonies per mL using the Countermat® software package.

The results will be recorded an electronic file created by the sponsor.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Data collection form (DCF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in DCF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or her designee.

A. Subject Inclusion Criteria

Subjects will be eligible for enrollment if they:

1. Are a male or female, over 18 years of age ;
2. Have signed a written informed consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/Dermatological/ Medical History Form (DCF 1);
4. Have hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders;
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

Subjects will not be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of arm or hand wash study within the past 7 days;
3. Have cuts, lesions, or other skin disorders on their hands or wrists;
4. Have soap, detergent, antibiotic, and/or perfume allergies;
5. Have eczema or psoriasis on their hands or arms;
6. Are using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos in the home within the last week (Appendix E);
7. Have excessively long or artificial nails (≥2 mm free edge) which would interfere with sampling;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator, would preclude participation.

D. Subject Number Assignment and Randomization

Upon entry into the study, each subject will be assigned a screening number beginning with 1001. Subjects will be assigned a permanent consecutive number, beginning with 001, as they are accepted into the study. This number will be used to identify the subject for the duration of the study.

IV. Study Material

A. Test Product

The test products will be sent by the Sponsor to the clinical site prior to study initiation. The test products will be identified with the appropriate label affixed to the outside of each container.

B. Shipping of Treatment Products and Other Study Supplies

The quantity of all treatment products and other study supplies, shipped to and returned from the clinical site, will be documented by the test site. The treatment products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc." with the facility's full

address and phone number);

3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator(s) will insure that all test products and study materials, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11520 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Kathy Wiandt

V. Other Study Documentation

A. Adverse Events

Should any unexpected or serious adverse event occur during the clinical study or as a result of test product or study procedures, the subject will be requested to return to the site to be examined by the investigator or designee. The Investigator will determine if the adverse event is likely to be associated with product treatment or the study procedures. The investigator or other qualified medical personnel will determine if the event warrants termination of participation and/or to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward L. Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Kathy Wiandt, 513-626-5225 (work) or 513-398-6035 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in DCF 4. If treatment by a physician is necessary, this treatment will be documented on DCF 5.

The following criteria will be used to determine the reporting time frame.

1. Any serious adverse events or adverse events requiring immediate medical attention will be reported to the Sponsor's Monitor immediately (night or day) by telephone.
2. Adverse events resulting in subject termination from the study will be reported during the immediate business day by telephone.
3. Adverse events that do not require discontinuation of test participation can be reported during the immediate business day or next business day by telephone.
4. In the event of a serious adverse reaction, not necessarily related to use of the test product, or in the event of a death from any cause, the Investigator must report the event to the Sponsor's Monitor.

B. Protocol Amendments

If it becomes necessary to modify this protocol, the modification will be documented by a protocol amendment signed by the investigator and a representative of the Sponsor. All amendments to the final protocol will be consecutively numbered and will describe any changes made and the rationale for making the changes.

C. Protocol Deviations

If a deviation from the final protocol occurs, it is the responsibility of the Investigator, or designee, to notify the Clinical Research Associate or designee. The deviation and subsequent notification will be documented appropriately.

D. Study Monitoring

The Investigator will permit a representative of the Sponsor (usually the Clinical Research Associate) to visit the facility during the course of the study to monitor study progress. During the visit(s), the Investigator will permit the monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The study monitor will also be permitted to review and verify test articles, wash procedure, and any Investigator-generated or Sponsor-generated study documents. The monitor will document and discuss this visit with the Investigator, or his designee, including any problems that are to be resolved.

VI. Statistical Analyses

The sponsor will be responsible for all statistical analyses. For the bag juice results, each subject's base sampling CFU's will be compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 will be considered statistically significant. Percent change for each organism will be computed , if needed, by the following formula:

$$1 - \frac{\text{(geometric mean of the test CFU's)}}{\text{geometric mean of the baseline CFU's}} \times 100$$

VII. Investigator Responsibilities

A. Subject Informed Consent

All subjects will be informed as to the type of study, the general nature of the products being tested, and any known or anticipated adverse reactions which might result from participation. Each subject must provide the Investigator with written informed consent to serve as a participant in the study. Basic elements of informed consent are outlined in 21 CFR 50.25.

B. Final Report

The Sponsor will generate a final report of clinical results. The investigator will provide a detailed description of the adverse events and deviations from the protocol. The investigator will also include an accounting of the subjects screened, eliminated, enrolled and terminated. The Investigator will submit the legible copies of all data collection forms. The Sponsor may request one (1) copy of all case report forms before the Investigator's report is ready for submission to the Sponsor.

C. Record Retention

The Investigator will retain all study records in accordance with the test facility's SOP's.

D. Confidentiality

The Investigator and employees of the test facility are obligated to keep any information confidential regarding any of the personal cleansing products and all aspects of the study, as subject to the terms and conditions of the Laboratory Services Agreement between the test facility and Sponsor.

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CP 14

Clinical Study Report

CRA: Kathy Wiandt **Date:** June 12, 2001

Study Statistician: Jeanne Philippo **Retention Limit:** Until Superseded

Approved by: WZB 6/26/01

Subject: Results of Efficacy Evaluation of Two Handsoap Products and Two Towlette Products in a Modified Healthcare Personnel Handwash Study Versus *Escherichia coli* – CRB-01-05-066-HB / HT# 01-108592-11.

Objective:

The objective of this study was to determine the ability of four antibacterial products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments. Treatment comparisons were made between the two handwipe products and between the two handwash products.

Materials Tested:

Test Code	Test Material	Active Ingredient	Master Formula Number
A	Handwash Product	0% Salicylic Acid	SWH160-152
B	Handwash Product	2% Salicylic Acid	SWH160-155
C	Handwipe Product	1% Salicylic Acid	SWH94-136
D	Handwipe Product	0% Salicylic Acid	SWH94-137

Key Conclusions:

- All four treatments significantly reduced the level of *E. coli* on the hands after one product application versus baseline.
- All four treatments significantly reduced the level of *E. coli* on the hands after ten product applications versus baseline.
- After one wash, the 2.0% Salicylic acid handwash product had a significantly higher reduction in log counts versus the test placebo (p-value=0.001).
- After ten washes, the 2.0% Salicylic acid handwash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0001).
- After one wash, there was no significant difference between the 1.0% Salicylic acid handwipe and the placebo handwipe product.
- After ten washes, the 1.0% Salicylic acid handwipe had a significantly higher reduction in log counts versus the test placebo (p-value=0.0044).

The summary of the mean logs recovered and the log reductions achieved following the first and tenth washes were determined.

Table I –Summary of HCPHWT Log_{10} Bacterial Results								
		Baseline	**Log_{10}Counts – 1 Wash**			**Log_{10}Counts – 10 Washes**		
Treatment	Sample Size	Mean	Mean	Change from Baseline	% Reduction	Mean	Change from Baseline	% Reduction
A-Handsoap 0% Salicylic Acid	16	6.72	3.91	2.80	99.84	3.80	2.92	99.88
B-Handsoap 2% Salicylic Acid	16	6.81	3.52	3.29	99.95	3.00	3.80	99.98
C-Handwipe 1% Salicylic Acid	16	6.66	4.22	2.44	99.64	3.48	3.18	99.93
D-Handwipe 0% Salicylic Acid	16	6.63	4.34	2.30	99.49	4.19	2.44	99.64

Attached are tables containing the statistical summary of the study results.

Study Summary:

Test Site: Hill Top Research, Miamiville, Ohio

Study Dates: May 22 – June 6, 2001

Investigator: Gayle K. Mulberry, M.S.

Experimental Design: This was a randomized clinical study consisting of a four day test period and a follow-up visit. Four test products were evaluated. Sixteen subjects were used to evaluate each product. Each subject participated in a single test day and a follow-up visit.

Efficacy Measurements Taken: The subjects' hands were contaminated with a suspension of *Escherichia coli* ATCC 11229. Subjects' hands were contaminated eleven times and sampled three times using a plastic bag sampling procedure. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after one treatment with the assigned test product. After eleven contamination steps and ten treatments with the assigned test product the hands were sampled using the plastic bag sampling procedure.

Subject Demographics: Sixty-four (64) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions or creams and or antidandruff shampoos were enrolled into the study. Sixteen subjects were used to evaluate one of four test products.

Overview: To become familiar with the wash procedure using a liquid hand soap, the subjects assigned to the handwash products practiced the wash procedure with Baby-san®. To become familiar with the wipe procedure, subjects assigned to the handwipe products practiced the wipe procedure with Nice 'n' Clean®. For the base count, subjects' hands were contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands were removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands were contaminated with *E. coli*. After completing the contamination step, the subjects performed the test product application procedure with the assigned test product. For the subjects assigned to the hand wash products, the subjects lathered their hands for fifteen seconds and rinsed their hands for thirty seconds. For the subjects assigned to the handwipe product, the subjects wiped each hand for fifteen seconds. Approximately five minutes following the product treatment procedure, the organisms on both of the subjects' hands were removed using a plastic bag sampling procedure. Approximately five minutes following the tenth treatment, the organisms on the subjects' hands were removed using a plastic bag sampling procedure

Samples of the subjects' sampling solutions were diluted, plated, and incubated. Following incubation, the numbers of colony forming units (CFU's) were enumerated. Antibacterial activity was determined by comparing the number of bacteria removed from the hands after one treatment with the assigned test product and ten treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

Data Analysis:

The investigator was responsible for statistical analysis. For the bag juice results, each subject's base sampling CFU's was compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.05 were considered statistically significant. Percent change for each organism was computed by the following formula:

$$1 - \left(\frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}} \right) \times 100$$

Treatment comparisons were analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

Regulatory/Ethics Status:

This study was conducted in compliance with federal, state, and local regulations, guidelines, and standards including those related to Informed Consent and Good Clinical Practices as specified under 21 CRF 321.66. This study was conducted with IRB approval.

Subject Accountability:

Eighty subjects were screened for the study. Sixty-four subjects were screened, enrolled and completed this study. Sixteen subjects were excluded from the study.

Adverse Events:

There was one adverse event in this study. Subject #35 reported a head cold on 6/5/01. The adverse event was not related to the product treatment. The adverse event was resolved on 6/19/01.

Clinical Research Associate

Statistician

HTR Study Number 01-108592-11

10:55 Wednesday, June 6, 2001

Table 1A. CFU count summary statistics by HTR Code.

HTR Code	Sample Size	Base Count Mean	Base Count Median	Base Count Std. Error	Test Count 1 Mean	Test Count 1 Median	Test Count 1 Std. Error	Test Count 2 Mean	Test Count 2 Median	Test Count 2 Std. Error
HTR Code A	16	6.07E+06	6.25E+06	7.62E+05	1.26E+04	1.15E+04	2.63E+03	7.60E+03	5.92E+03	1.26E+03
HTR Code B	16	6.93E+06	7.35E+06	5.91E+05	4.19E+03	3.62E+03	5.49E+02	1.68E+03	1.38E+03	3.69E+02
HTR Code C	16	5.82E+06	6.46E+06	7.68E+05	3.76E+04	3.53E+04	9.42E+03	9.54E+03	4.84E+03	3.51E+03
HTR Code D	16	4.78E+06	4.31E+06	5.03E+05	3.73E+04	3.27E+04	6.87E+03	2.57E+04	1.76E+04	5.93E+03

Table 1B. Log10(Count) summary statistics by HTR Code.

HTR Code	Sample Size	Base Count Mean	Base Count Median	Base Count Std. Error	Test Count 1 Mean	Test Count 1 Median	Test Count 1 Std. Error	Test Count 2 Mean	Test Count 2 Median	Test Count 2 Std. Error
HTR Code A	16	6.7168	6.7957	0.0656	3.9120	4.0203	0.1128	3.7950	3.7580	0.0627
HTR Code B	16	6.8064	6.8648	0.0441	3.5155	3.5559	0.0950	3.0042	3.1257	0.1168
HTR Code C	16	6.6587	6.8059	0.0963	4.2173	4.5297	0.1944	3.4826	3.6610	0.2040
HTR Code D	16	6.6329	6.6197	0.0481	4.3366	4.4844	0.1433	4.1915	4.2367	0.1230

Table 1C. Log10 changes from baseline summary statistics and percent reductions.

HTR Code	Test Count 1 Sample Size	Test Count 1 Mean Change	Test Count 1 Median Change	Test Count 1 Std. Error Change	Test Count 1 Percent Reduction	Test Count 2 Sample Size	Test Count 2 Mean Change	Test Count 2 Median Change	Test Count 2 Std. Error Change	Test Count 2 Percent Reduction
HTR Code A	[illegible]	[illegible]	[illegible]	0.0651	[illegible]	[illegible]	[illegible].9218	2.9099	0.0647	99.88
HTR Code B	[illegible]	[illegible]	3.2920	0.1011	[illegible]	[illegible]	3.8021	3.7333	0.1223	99.98
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	3.1[illegible]61	3.1729	0.1628	99.93
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible].4411	[illegible].4788	0.1196	99.64

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code A	1	6.25E+06	6.00E+06	6.13E+06	1.96E+04	1.44E+04	1.70E+04	7.57E+03	7.52E+03	7.55E+03
	7	4.15E+06	4.40E+06	4.28E+06	5.26E+03	3.76E+03	4.51E+03	7.27E+03	4.30E+03	5.79E+03
	11	8.65E+06	9.50E+06	9.08E+06	2.14E+04	1.86E+04	2.00E+04	1.86E+04	1.15E+04	1.51E+04
	14	2.35E+06	2.18E+06	2.27E+06	2.09E+03	5.03E+03	3.56E+03	2.80E+03	6.69E+03	4.75E+03
	17	8.15E+06	5.55E+06	6.85E+06	1.93E+04	7.08E+03	1.32E+04	1.14E+04	9.80E+03	1.06E+04
	24	2.95E+06	3.85E+06	3.40E+06	8.50E+02	2.32E+03	1.59E+03	5.38E+03	3.19E+03	4.29E+03
	27	2.52E+06	2.25E+06	2.39E+06	1.15E+03	1.46E+03	1.31E+03	5.37E+03	3.03E+03	4.20E+03
	32	7.20E+06	9.30E+06	8.25E+06	9.00E+03	9.80E+03	9.40E+03	5.45E+03	2.93E+03	4.19E+03
	34	6.40E+06	6.35E+06	6.38E+06	6.46E+03	6.88E+03	6.67E+03	5.71E+03	4.38E+03	5.05E+03
	38	1.38E+07	1.16E+07	1.27E+07	4.60E+04	3.95E+04	4.28E+04	1.96E+04	2.48E+04	2.22E+04
	44	9.90E+06	9.20E+06	9.55E+06	2.45E+04	1.23E+04	1.84E+04	7.44E+03	1.40E+04	1.07E+04
	48	4.50E+06	6.15E+06	5.33E+06	5.49E+03	1.42E+04	9.85E+03	4.56E+03	7.55E+03	6.06E+03
	50	6.65E+06	9.35E+06	8.00E+06	2.07E+04	2.05E+04	2.06E+04	6.77E+03	8.85E+03	7.81E+03
	53	5.35E+06	3.30E+06	4.33E+06	1.56E+04	1.34E+04	1.45E+04	2.26E+03	2.96E+03	2.61E+03
	59	6.55E+06	7.25E+06	6.90E+06	1.58E+04	1.61E+04	1.60E+04	1.55E+03	5.84E+03	3.70E+03
	62	1.24E+06	1.45E+06	1.35E+06	1.61E+03	2.37E+03	1.99E+03	6.40E+03	7.65E+03	7.03E+03
HTR Code A		6.04E+06	6.11E+06	6.07E+06	1.34E+04	1.17E+04	1.26E+04	7.38E+03	7.81E+03	7.60E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code B	4	5.40E+06	4.10E+06	4.75E+06	6.38E+03	6.08E+03	6.23E+03	9.40E+02	1.87E+03	1.41E+03
	6	1.30E+07	1.14E+07	1.04E+07	9.40E+03	8.15E+03	8.78E+03	3.97E+03	3.75E+03	3.86E+03
	10	[illegible]	[illegible]	[illegible]	3.54E+03	4.14E+03	[illegible]	1.46E+03	1.24E+03	1.35E+03
	16	[illegible]	[illegible]	[illegible]	5.31E+03	1.45E+03	[illegible]	1.28E+03	1.60E+02	7.20E+02
	19	6.45E+06	9.05E+06	7.75E+06	1.99E+03	3.36E+03	2.68E+03	2.61E+03	2.06E+03	2.34E+03
	22	4.90E+06	7.25E+06	6.08E+06	7.20E+03	5.70E+03	6.45E+03	3.57E+03	5.94E+03	4.76E+03
	26	4.55E+06	5.10E+06	4.83E+06	2.45E+03	1.39E+03	1.92E+03	5.93E+03	3.02E+03	4.48E+03
	29	8.50E+06	9.60E+06	9.05E+06	1.80E+03	4.65E+03	3.23E+03	1.04E+03	4.10E+02	7.25E+02
	35	9.35E+06	9.20E+06	9.28E+06	2.12E+03	2.83E+03	2.48E+03	4.30E+02	1.80E+02	3.05E+02
	40	6.80E+06	8.35E+06	7.58E+06	5.07E+03	1.81E+03	3.44E+03	9.50E+02	2.21E+03	1.58E+03
	43	7.50E+06	9.80E+06	8.65E+06	3.89E+03	2.44E+03	3.17E+03	6.50E+02	2.30E+02	4.40E+02
	47	2.26E+06	3.30E+06	2.78E+06	4.72E+03	4.69E+03	4.71E+03	1.28E+03	4.20E+02	8.50E+02
	51	6.85E+06	7.40E+06	7.13E+06	3.11E+03	4.04E+03	3.58E+03	8.00E+01	1.60E+02	1.20E+02
	54	5.85E+06	5.35E+06	5.60E+06	4.06E+03	3.28E+03	3.67E+03	1.77E+03	1.92E+03	1.85E+03
	57	1.06E+07		1.06E+07	5.50E+03	9.75E+03	7.63E+03	1.24E+03	2.24E+03	1.74E+03
	64	3.65E+06	7.95E+06	5.80E+06	1.10E+02	3.20E+02	2.15E+02	1.80E+02	5.70E+02	3.75E+02
HTR Code B		6.34E+06	7.32E+06	6.93E+06	4.17E+03	4.21E+03	4.19E+03	1.71E+03	1.65E+03	1.68E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code C	2	3.04E+06	2.71E+06	2.88E+06	6.60E+03	1.24E+04	9.50E+03	3.69E+03	7.34E+03	5.52E+03
	5	6.10E+06	8.15E+06	7.13E+06	5.15E+04	6.70E+04	5.93E+04	2.12E+04	1.36E+04	1.74E+04
	9	8.70E+06	7.45E+06	8.08E+06	3.00E+04	7.95E+04	5.48E+04	3.03E+03	5.15E+03	4.09E+03
	13	2.58E+06	2.44E+06	2.51E+06	2.42E+03	3.00E+02	1.36E+03	1.96E+03	5.40E+02	1.25E+03
	18	3.60E+06	3.80E+06	3.70E+06	3.70E+04	2.42E+04	3.06E+04	8.20E+03	6.55E+03	7.38E+03
	23	2.70E+05	3.30E+05	3.00E+05	9.30E+02	2.00E+01	4.75E+02	4.00E+01	1.00E+02	7.00E+01
	25	7.60E+06	8.15E+06	7.88E+06	6.50E+04	2.70E+04	4.60E+04	5.95E+04	4.95E+04	5.45E+04
	31	5.70E+06	5.20E+06	5.45E+06	2.27E+04	1.33E+04	1.80E+04	7.70E+02	4.30E+02	6.00E+02
	33	2.37E+06	2.02E+06	2.20E+06	3.40E+04	5.15E+04	4.28E+04	4.80E+03	6.74E+03	5.77E+03
	39	5.85E+06	8.05E+06	6.95E+06	5.25E+04	2.70E+04	3.98E+04	5.80E+02	5.70E+02	5.75E+02
	41	5.25E+06	9.90E+06	7.58E+06	1.16E+04	5.66E+03	8.63E+03	3.11E+03	5.23E+03	4.17E+03
	46	8.55E+06	9.75E+06	9.15E+06	4.25E+04	7.70E+04	5.98E+04	1.21E+04	1.30E+04	1.26E+04
	52	3.00E+06	3.00E+06	3.00E+06	3.54E+03	3.61E+03	3.58E+03	1.70E+02	9.00E+01	1.30E+02
	55	6.40E+06	5.55E+06	5.98E+06	1.22E+05	1.90E+05	1.56E+05	2.67E+04	2.76E+04	2.72E+04
	58	8.75E+06	9.60E+06	9.18E+06	4.30E+04	3.24E+04	3.77E+04	3.50E+03	1.20E+03	2.35E+03
	61	1.24E+07	9.85E+06	1.11E+07	4.45E+04	2.12E+04	3.29E+04	1.10E+04	7.22E+03	9.11E+03
HTR Code C		5.64E+06	6.00E+06	5.82E+06	3.56E+04	3.95E+04	3.76E+04	1.00E+04	9.05E+03	9.54E+03

Table 2A. Listing of CFU/ml counts by HTR Code.

HTR Code	Subject	Base Count Left CFU/ml	Base Count Right CFU/ml	Base Count Avg. CFU/ml	Test Count 1 Left CFU/ml	Test Count 1 Right CFU/ml	Test Count 1 Avg. CFU/ml	Test Count 2 Left CFU/ml	Test Count 2 Right CFU/ml	Test Count 2 Avg. CFU/ml
HTR Code D	3	[illegible]	[illegible]	[illegible]	1.02E+05	5.25E+04	7.73E+04	2.83E+03	2.38E+03	2.61E+03
	8	[illegible]	9.35E+06	8.05E+06	5.95E+04	9.05E+04	7.50E+04	9.70E+04	5.05E+04	7.38E+04
	12	[illegible]	3.27E+06	[illegible]	3.70E+04	2.78E+04	[illegible]	3.15E+04	3.70E+04	3.43E+04
	15	[illegible]	[illegible]	[illegible]	[illegible]	4.05E+04	[illegible]	[illegible]	2.75E+04	2.51E+04
	20	[illegible]	[illegible]	[illegible]	5.25E+04	1.30E+04	[illegible]	[illegible]	2.22E+04	2.43E+04
	21	5.30E+06	6.50E+06	5.90E+06	5.15E+04	4.25E+04	4.70E+04	2.17E+04	1.82E+04	2.00E+04
	28	3.40E+06	3.05E+06	3.23E+06	1.46E+04	6.08E+03	1.03E+04	1.10E+04	1.00E+04	1.05E+04
	30	5.90E+06	6.10E+06	6.00E+06	4.25E+03	1.51E+04	9.68E+03	1.28E+04	1.75E+04	1.52E+04
	36	3.85E+06	3.65E+06	3.75E+06	2.53E+04	2.50E+04	2.52E+04	1.00E+04	9.05E+03	9.53E+03
	37	5.05E+06	7.15E+06	6.10E+06	4.30E+04	7.30E+04	5.80E+04	5.05E+04	6.70E+04	5.88E+04
	42	2.75E+06	3.38E+06	3.07E+06	6.59E+03	2.59E+03	4.59E+03	1.25E+03	1.44E+03	1.35E+03
	45	6.40E+06	8.20E+06	7.30E+06	3.90E+04	6.75E+04	5.33E+04	1.74E+04	1.20E+04	1.47E+04
	49	2.44E+06	3.50E+06	2.97E+06	1.16E+04	1.16E+04	1.16E+04	4.51E+03	7.29E+03	5.90E+03
	56	5.55E+06	3.80E+06	4.68E+06	1.20E+05	6.00E+04	9.00E+04	4.85E+04	2.35E+04	3.60E+04
	60	6.45E+06	6.75E+06	6.60E+06	5.35E+04	2.04E+04	3.70E+04	7.35E+03	6.34E+03	6.85E+03
	63	1.61E+06	2.21E+06	1.91E+06	1.20E+02	2.34E+03	1.23E+03	9.20E+04	5.35E+04	7.28E+04
HTR Code D		4.24E+06	5.32E+06	4.78E+06	4.01E+04	3.44E+04	3.73E+04	2.86E+04	2.28E+04	2.57E+04

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 1 Left Log10 CFU/ml	Test Count 1 Right Log10 CFU/ml	Test Count 1 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code A	1	4.2923	4.1584	4.2253	2.5617	
	7	3.7210	3.5752	3.6481	2.9827	
	11	4.3304	4.2695	4.3000	2.6574	
	14	3.3201	3.7016	3.5109	2.8439	
	17	4.2856	3.8500	4.0678	2.7599	
	24	2.9294	3.3655	3.1475	3.3802	
	27	3.0607	3.1644	3.1125	3.2643	
	32	3.9542	3.9912	3.9727	2.9402	
	34	3.8102	3.8376	3.8239	2.9806	
	38	4.6628	4.5966	4.6297	2.4725	
	44	4.3892	4.0899	4.2395	2.7402	
	48	3.7396	4.1523	3.9459	2.7751	
	50	4.3160	4.3118	4.3139	2.5830	
	53	4.1931	4.1271	4.1601	2.4633	
	59	4.1987	4.2068	4.2027	2.6355	
	62	3.2068	3.3747	3.2908	2.8366	0.0001*
HTR Code A		3.9006	3.9233	3.9120	2.8048	0.0001*

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 2 Left Log10 CFU/ml	Test Count 2 Right Log10 CFU/ml	Test Count 2 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code A	1	3.8791	3.8762	3.8777	2.9094	
	7	3.8615	3.6335	3.7475	2.8832	
	11	4.2695	4.0607	4.1651	2.7923	
	14	3.4472	3.8254	3.6363	2.7185	
	17	4.0569	3.9912	4.0241	2.8037	
	24	3.7308	3.5038	3.6173	2.9104	
	27	3.7300	3.4814	3.6057	2.7711	
	32	3.7364	3.4669	3.6016	3.3113	
	34	3.7566	3.6415	3.6991	3.1054	
	38	4.2923	4.3945	4.3434	2.7588	
	44	3.8716	4.1461	4.0089	2.9709	
	48	3.6590	3.8779	3.7685	2.9526	
	50	3.8306	3.9469	3.8888	3.0081	
	53	3.3541	3.4713	3.4127	3.2107	
	59	3.1903	3.7664	3.4784	3.3599	
	62	3.8062	3.8837	3.8449	2.2825	0.0001*
HTR Code A		3.7795	3.8105	3.7950	2.9218	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 1 Left Log10 CFU/ml	Test Count 1 Right Log10 CFU/ml	Test Count 1 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code B	4	3.8048	3.7839	3.7944	2.8782	
	6	3.9731	3.9112	3.9421	3.0706	
	10	3.5490	3.6474	3.5982	3.2812	
	16	3.7251	3.6464	3.6857	2.7840	
	19	3.2989	3.5263	3.4126	3.4705	
	22	3.8573	3.7559	3.8066	2.9687	
	26	3.3892	3.1430	3.2661	3.4167	
	29	3.2553	3.6675	3.4614	3.4945	
	35	3.3263	3.4518	3.3891	3.5782	
	40	3.7050	3.2577	3.4813	3.3958	
	43	3.5899	3.3874	3.4887	3.4445	
	47	3.6739	3.6712	3.6726	2.7638	
	51	3.4928	3.6064	3.5496	3.3029	
	54	3.6085	3.5159	3.5622	3.1856	
	57	3.7404	3.9890	3.8647	3.1606	
	64	2.0414	2.5051	2.2733	4.4581	0.0001*
HTR Code B		3.5019	3.5291	3.5155	3.2909	0.0001*

HTR Code	Subject	Test Count 2 Left Log10 CFU/ml	Test Count 2 Right Log10 CFU/ml	Test Count 2 Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code B	4	2.9731	3.2718	3.1225	3.5501	
	6	3.5988	3.5740	3.5864	3.4263	
	10	3.1644	3.0934	3.1289	3.7505	
	16	3.1072	2.2041	2.6557	3.8141	
	19	3.4166	3.3139	3.3653	3.5179	
	22	3.5527	3.7738	3.6632	3.1120	
	26	3.7731	3.4800	3.6265	3.0563	
	29	3.0170	2.6128	2.8149	4.1409	
	35	2.6335	2.2553	2.4444	4.5229	
	40	2.9777	3.3444	3.1611	3.7160	
	43	2.8129	2.3617	2.5873	4.3458	
	47	3.1072	2.6232	2.8652	3.5711	
	51	1.9031	2.2041	2.0536	4.7989	
	54	3.2480	3.2833	3.2656	3.4821	
	57	3.0934	3.3502	3.2218	3.8035	
	64	2.2553	2.7559	2.5056	4.2258	0.0001*
HTR Code B		3.0396	2.9689	3.0042	3.8021	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

		Test Count 1				
HTR Code	Subject	Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code C	2	3.8195	4.0934	3.9565	2.5014	
	5	4.7118	4.8261	4.7689	2.0793	
	9	4.4771	4.9004	4.6887	2.2171	
	13	3.3838	2.4771	2.9305	3.4690	
	18	4.5682	4.3838	4.4760	2.0920	
	23	2.9685	1.3010	2.1348	3.3402	
	25	4.8129	4.4314	4.6221	2.2738	
	31	4.3560	4.1239	4.2399	2.4960	
	33	4.5315	4.7118	4.6216	1.7184	
	39	4.7202	4.4314	4.5758	2.2607	
	41	4.0645	3.7528	3.9086	2.9493	
	46	4.6284	4.8865	4.7574	2.2030	
	52	3.5490	3.5575	3.5533	2.9239	
	55	5.0864	5.2788	5.1826	1.5927	
	58	4.6335	4.5105	4.5720	2.3901	
	61	4.6484	4.3263	4.4873	2.5561	0.0001*
HTR Code C		4.3100	4.1245	4.2173	2.4414	0.0001*

		Test Count 2				
HTR Code	Subject	Left Log10 CFU/ml	Right Log10 CFU/ml	Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code		4.5670	3.8657	3.7161	2.7416	
	5	4.3263	4.1335	4.2299	2.6183	
	9	3.4814	3.7118	3.5966	3.3092	
	13	3.2923	2.7324	3.0123	3.3872	
	18	3.9138	3.8162	3.8650	2.7030	
	23	1.6021	2.0000	1.8010	3.6739	
	25	4.7745	4.6946	4.7346	2.1614	
	31	2.8865	2.6335	2.7600	3.9760	
	33	3.6812	3.8287	3.7550	2.5851	
	39	2.7634	2.7559	2.7597	4.0768	
	41	3.4928	3.7185	3.6056	3.2523	
	46	4.0828	4.1139	4.0984	2.8621	
	52	2.2304	1.9542	2.0923	4.3848	
	55	4.4265	4.4409	4.4337	2.3415	
	58	3.5441	3.0792	3.3116	3.6505	
	61	4.0414	3.8585	3.9500	3.0935	0.0001*
HTR Code C		3.5067	3.4586	3.4826	3.1761	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 2B. Listing of Log10 counts and results of the Wilcoxon Paired Sign Rank Test.

HTR Code	Subject	Test Count 1: Left Log10 CFU/ml	Test Count 1: Right Log10 CFU/ml	Test Count 1: Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code D	3	5.0086	4.7202	4.8644	1.5410	
	8	4.7745	4.9566	4.8656	2.0345	
	12	4.5682	4.4440	4.5061	1.9224	
	15	4.3181	4.6075	4.4628	2.3777	
	20	4.7202	4.1335	4.4268	2.1505	
	21	4.7118	4.6284	4.6701	2.0985	
	28	4.1644	3.7839	3.9741	2.5338	
	30	3.6284	4.1790	3.9037	2.8744	
	36	4.4031	4.3979	4.4005	2.1733	
	37	4.6335	4.8633	4.7484	2.0304	
	42	3.8189	3.4133	3.6161	2.8680	
	45	4.5911	4.8293	4.7102	2.1498	
	49	4.0645	4.0645	4.0645	2.4013	
	56	5.0792	4.7782	4.9287	1.7334	
	60	4.7284	4.3096	4.5190	2.3004	
	63	2.0792	3.3692	2.7242	3.5514	0.0001*
HTR Code D		4.3307	4.3424	4.3366	2.2963	0.0001*

HTR Code	Subject	Test Count 2: Left Log10 CFU/ml	Test Count 2: Right Log10 CFU/ml	Test Count 2: Avg. Log10 CFU/ml	Log Diff. (Base-Test)	Wilcoxon p-value
HTR Code D	3	3.4518	3.3766	3.4142	2.9912	
	8	[illegible]	4.7033	4.8450	2.0550	
	[illegible]	[illegible]	[illegible]	4.5333	[illegible]	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	20	[illegible]	4.3464	4.3832	2.1942	
	21	4.3365	4.2601	4.2983	2.4703	
	28	4.0414	4.0000	4.0207	2.4872	
	30	4.1072	4.2430	4.1751	2.6030	
	36	4.0000	3.9566	3.9783	2.5956	
	37	4.7033	4.8261	4.7647	2.0141	
	42	3.0969	3.1584	3.1276	3.3565	
	45	4.2405	4.0792	4.1599	2.7001	
	49	3.6542	3.8627	3.7585	2.7073	
	56	4.6857	4.3711	4.5284	2.1336	
	60	3.8663	3.8021	3.8342	2.9852	
	63	4.9638	4.7284	4.8461	1.4295	0.0001*
HTR Code D		4.2129	4.1701	4.1915	2.4414	0.0001*

Positive difference indicates reduction from baseline.
* Indicates significance

Table 3. Results of the Wilcoxon-Mann-Whitney Test for the between treatment analysis of test articles.

Group	-Test Count 1-- p-value	-Test Count 2-- p-value
A vs B	0.0010*	0.0001*
C vs D	0.3080	0.0044*

* indicates significant difference between treatments

HTR Study No.: 01-108592-11
Sponsor Study No.: CRB-01-05-066-HB

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of Hill Top Research, Inc. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records.

Data reviewed by:

Thomas Asplan, A.A.S., B.S. — Date
Auditor, Quality Assurance

CLINICAL STUDY PROTOCOL

Clinical Research & Biometrics Department
Sharon Woods Technical Center
Cincinnati, Ohio 45241

Title:	Efficacy Evaluation Of Two Liquid Soap Products and Two Towelette Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*
Study Number:	CRB-01-05-066-HB / HT# 01-108592-11
Issue Date:	5/15/01
Products Tested:	Antibacterial Handsoap Prototype (2% Salicylic Acid) Control Handsoap Prototype (0% Salicylic Acid) Antibacterial Handwipe Prototype (1% Salicylic Acid) Control Handwipe Prototype (0% Salicylic Acid)
Test Facility:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Principal Investigator:	Gayle Mulberry, M.S.
Sub-Investigators:	Kathleen A. Baxter, B.S. Ann R. Brady, A.S.
Test Sponsor:	The Procter & Gamble Co., Inc. Sharon Woods Technical Center 11520 Reed Hartman Highway Cincinnati, Ohio 45241

		work	home
Sponsor Toxicologist:	Candace Doepker, Ph.D.	(513) 626-5536	
	Tim Long, Ph.D	(513) 626-4027	
Sponsor Representative/CRA:	Kathy Wiandt, B.A	(513) 626-5225	(513) 398-6035
Sponsor Statistician:	Jeanne Philippo, B.A.	(513) 626-5937	

Expected Study Start Date:	May 22, 2001
Expected Study End Date:	June 6, 2001

I. Study Objective and Background

A. Objective

The objective of the study is to determine the ability of four antibacterial products to significantly reduce transient microbial flora (*Escherichia coli* ATCC 11229) on the hands after a single treatment and after ten (10) treatments. Treatment comparisons will be made between the two handwipe products and between the two handwash treatments.

B. Background

The skin microflora can be divided into two (2) groups, the resident flora and the transient flora. The resident flora includes organisms that are consistently present on the skin. The transient flora are the contaminating skin organisms resulting from contact with the environment. They comprise a wide variety of Gram positive and Gram negative species that can be responsible for the spread of infections and gastrointestinal diseases.

Since the benefits that result from washing with antibacterial soaps can not be easily measured under consumer use conditions, it is necessary to do controlled clinical studies to demonstrate their efficacy. This clinical study is a modification of an ASTM test method, "Evaluation of Health Care Personnel Handwash Formulation"(1) and reported in the Tentative Final Monograph for Health Care Antiseptic Drug Products(2). It is used to determine the ability of an antimicrobial handwashing agent, when used in a hand washing procedure, to reduce the transient microbial flora (contaminants). This study is designed to demonstrate the efficacy of four antibacterial products in reducing the numbers of a marker organism, *Escherichia coli* ATCC 11229 on the hands after a contamination and a single handwash and after ten handwashes. Efficacy is determined by comparing the numbers of marker organisms on the hands before and after using the test products.

C. Study Safety Statement

This testing meets the ethical requirements stipulated in the Sponsor's Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

II. Study Summary

A. Overview

This randomized clinical study will consist of a four day test period and a follow-up visit. Four (4) test products will be evaluated. Sixty-four (64) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and or antidandruff shampoos (Appendix E), will be enrolled into the study. Sixteen (16) subjects will be used to evaluate each test product.

On the day of the study, the subjects will report to the clinical test facility. During this period, subjects' hands will be contaminated with a suspension of *E.coli*. Subjects' hands will be contaminated eleven (11) times and sampled three (3) times using a plastic bag sampling procedure. The first contamination and sampling will be for the determination of the base count. The second contamination and sampling will be for determination of the test count after one (1) treatment with the assigned Test Product. After eleven (11) contamination steps and ten (10) treatments with the assigned Test Products the hands will be sampled using the plastic bag sampling procedure

To become familiar with the wash procedure using the liquid hand soap, subjects assigned to handwash products will begin the test procedure by first performing a practice wash with Baby-san®. To become familiar with the wipe procedure using the towelette products, subjects assigned to handwipe products will begin the test procedure by first performing a practice wipe with Nice 'n' Clean®. For the base count, subjects will have their hands contaminated with *E. coli*. Immediately

following the contamination step, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands will be contaminated with *E. coli*. After completing the contamination step, the subjects will perform the test product application procedure with the assigned Test Product. Approximately five (5) minutes following the first procedure, the organisms on both of the subjects' hands will be removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Aliquots of the subjects' sampling solutions will be diluted, plated, and incubated. Following incubation, the number of colony forming units (CFU's) will be enumerated. Antibacterial activity is determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

B. Study Schedule

1. Subject Qualification and Enrollment

Prospective subjects will visit the test facility to be screened for their eligibility to participate in the study. Eligibility will be based upon information provided in the Demographics/Dermatological/ Medical History Form (DCF 1) and the Inclusion/Exclusion Form (DCF 2); and completion of a written informed consent (Appendix A).

2. Test Period

Subjects continuing on the study will be assigned a permanent subject number. Subjects will be assigned to one of the four test products according to the study randomization.

The following outlines the schedule of procedures for the test day:

1. Subjects will perform a practice wash with Baby-san® Handsoap or Nice "n' Clean® Handwipe(Appendix D).
2. Subjects will rinse their hands with 70% alcohol and rinse their hands under running tap water (Section G).
3. Subjects' hands will be contaminated (Section E).
4. Subjects' hands will be sampled for a base count (Section F).
5. Subjects will rinse their hands with water for 30 seconds (Section G).
6. Subjects will rinse their hands with 70% alcohol and rinse with tap water (Section G).
7. Subjects' hands will be contaminated (Section E).
8. Subjects will wash their hands following the wash procedure for the assigned Test Product (Section C, Appendix C).
9. Subjects' right and left hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds $\pm$ thirty (30) seconds after the first wash with the assigned Test Product (Section F).
10. The hands will be rinsed for thirty seconds.
11. Subjects will perform steps 7 and 8 (above) a total of nine (9) more times at a minimum of five (5) minutes between each wash procedure.
12. The subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds $\pm$ thirty (30) seconds after the tenth wash with the assigned Test Product (Section F).
13. Subjects' hands will be disinfected with a bland soap and water wash and Hibiclens® (4%

chlorhexidine gluconate) wash and with a 70% alcohol rinse (Section G).

Note: A detailed scheduled of the above procedures can be found in Appendix D.

To ensure that any delayed adverse events, such as primary skin infections, are reported to the Study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study Completion (Appendix B) before leaving the clinical site after they have completed the study. This sheet will instruct the subjects to examine their hands and wrists daily until the final scheduled visit for the presence of pimples, blisters, or raised, red itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection. Subjects, who notice such lesions, will be instructed to call the clinical test site. The subjects will return to the clinical test site within four (4) to nine (9) days after the study procedures have been completed to have their hands and wrists examined by a technician. The technician will complete DCF 3 for each subject on their follow-up visit.

C. Product Treatment Procedure

Subjects will wash their hands and wrists according to the procedure described in Product Treatment Procedure, Appendix C. In general the following should be noted:

- The temperature should be checked and recorded before each wash.
- The water pressure at each spigot to be used for the study should flow at 4 L/min.
- Subjects should remove all jewelry from hands and wrists prior to start of wash procedure.
- Water temperature should be maintained at 95 - 100° F.

D. Preparation of Bacterial Suspensions

A stock culture of *Escherichia coli*, ATCC 11229, will be prepared by transferring three (3) isolated colonies from an agar plate or slant aseptically to a tube containing sterile Trypticase Soy Broth (TSB). The inoculated broth will then be incubated for 24 ± 4 hours at 35 ± 2° C. At least three (3) additional 24 hour broth transfers will be made in tubes containing appropriate volumes TSB from this broth culture.

A 2-liter flask containing 1000 mL of TSB will be inoculated with 1.0 mL of the final 24 hour broth transfer. The flask will be incubated for 24 ± 4 hours at 35 ± 2° C. Prior to any withdrawal of culture, whether for hand contamination or for numbers assay, the suspension will be stirred or shaken. The suspension will be assayed for number of organisms at the beginning and end of the treatment period. A suspension will not be used for more than eight (8) hours.

E. Contamination

Note: Prior to contamination, subjects hands must be visibly dry. Also, care should be taken to ensure that the culture is evenly spread over both hands

A total volume of 4.5 mL of the assigned bacterial suspension will be dispensed into the subjects' cupped hands in 1.5 mL increments. After each 1.5 mL aliquot is added, the suspension will be rubbed thoroughly over the surface of both hands, not going above the wrist and avoiding the nail beds. Each application and spreading should last approximately twenty (20) seconds. Between each aliquot the hands will be held away from the body and allowed to air dry for approximately thirty (30) seconds. Following the third 1.5 mL aliquot, the hands are allowed to air dry for approximately one (1) minute. A record of base and test contaminations will be documented on Source Document 1 or 2.

F. Bacterial Sampling Procedure

For removal of bacteria from the subjects' hands, loose fitting plastic bags with low bioburden will be placed on each subject's right and left hands. A 75 mL aliquot of stripping solution [0.1% Triton X-100 in 0.075 M phosphate buffer, 1.0% polysorbate (Tween) 80, 0.3% Lecithin, pH 7.9] will be aseptically added into each bag. The same solution will be used for the base counts and test counts.

The bag on each hand will be secured at the wrist with a child's size tourniquet and massaged for one (1) minute in a uniform manner by a lab technician. Aliquots of the solution will be aseptically obtained directly from the bag without touching the hands in the process and will be appropriately diluted in a sterile diluent with the appropriate neutralizer within in one (1) minute of sampling. A record of base and test samplings will be documented on Source Document 1.

The solution samples for bacteria counts will be labeled by either an Investigator derived code or the actual subject's number so that the individuals who prepare the plates and count the CFU's are unaware of the sources of the sampling solution.

G. Disinfection of Hands

After the baseline sampling, the subjects will rinse their hands for thirty (30) seconds under running tap water. The subjects' hands will be disinfected with a 70% alcohol wash. Subjects' hands will be squirted with 70% alcohol for approximately ten (10) seconds. Subjects will rub the alcohol over the surface of their hands and wrists for approximately fifteen (15) seconds. Subjects will rinse their hands and wrists under running tap water for approximately fifteen (15) seconds and dry their hands and wrists with paper towels.

After the final sampling is completed, the subject's hands will be washed with a bland soap (provided by the investigator) for approximately for thirty (30) seconds and rinsed for approximately fifteen (15) seconds. The subjects' hands will then be washed with Hibiclens® (4% chlorhexidine gluconate) for at least sixty (60) seconds. Subjects' hands and wrists will be rinsed with a 70% alcohol wash for ten (10) seconds. The subjects will rub the alcohol on all surfaces of their hands for fifteen (15) seconds and allow their hands to air dry.

A record of each disinfection procedure will be recorded on Source Document 1.

H. Plating and Incubation of the Organisms

The *Escherichia coli* organisms in the sampling solution are to be counted using a standard surface inoculation technique.

Aliquots of dilutions of the base sampling solution from each sample bag representing dilutions of 10^{-4}, 10^{-5}, and 10^{-6} will be plated in duplicate.

Following the wash with the test product, a 1.0 mL aliquot of the previously diluted sampling solution from each sample bag will be plated onto three MacConkey's agar plates (approximately 0.33 mL per plate) to achieve a 10^{-1} dilution. Also, aliquots of dilutions of the sampling solution from each sample bag representing dilutions of 10^{-2}, 10^{-3}, 10^{-4} and 10^{-5} will be plated in duplicate. The MacConkey's agar plates will be incubated 18-24 hours at 35 ± 2°C. Standard plate counting procedures will be used to count the CFU's of *E. coli*. In general, the number of CFU's per sample will be determined by taking the average of the counts from the plates which are in the range of ≥ 25 to ≤ 250 CFU's. If there are no plates with counts within this range, the following rules will be used to determine which counts will be used for obtaining the number of CFU's for that specimen:

1. If all of the counts are below the prescribed range, the numbers below 25 from the undiluted plates will be used.

2. If the counts from the highest dilution are > 250, the numbers, obtained from using the estimated counting procedure described in Appendix F, will be used.

Results will be reported on DCF 4.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Data collection form (DCF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in DCF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or her designee.

A. Subject Inclusion Criteria

Subjects will be eligible for enrollment if they:

1. Are a male or female, over 18 years of age;
2. Have signed a written informed consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/Dermatological/ Medical History Form (DCF 1);
4. Have hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders;
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

Subjects will not be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of arm or hand wash study within the past 7 days;
3. Have cuts, lesions, or other skin disorders on their hands or wrists;
4. Have soap, detergent, antibiotic, and/or perfume allergies;
5. Have eczema or psoriasis on their hands or arms;
6. Are using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos in the home within the last week (Appendix E);
7. Have excessively long or artificial nails (≥2 mm free edge) which would interfere with sampling;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator, would preclude participation.

D. Subject Number Assignment and Randomization

Upon entry into the study, each subject will be assigned a screening number beginning with 1001. Subjects will be assigned a permanent consecutive number, beginning with 001, as they are accepted into the study. This number will be used to identify the subject for the duration of the study.

IV. Study Material

A. Test Product

The test products will be sent by the Sponsor to the clinical site prior to study initiation. The test products will be identified with the appropriate label affixed to the outside of each container.

B. Shipping of Treatment Products and Other Study Supplies

The quantity of all treatment products and other study supplies, shipped to and returned from the clinical site, will be documented by the test site. The treatment products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc." with the facility's full address and phone number);
3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator(s) will insure that all test products and study materials, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11520 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Kathy Wiandt

V. Other Study Documentation

A. Adverse Events

Should any unexpected or serious adverse event occur during the clinical study or as a result of test product or study procedures, the subject will be requested to return to the site to be examined by the investigator or designee. The Investigator will determine if the adverse event is likely to be associated with product treatment or the study procedures. The investigator or other qualified medical personnel will determine if the event warrants termination of participation and/or to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward L. Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Kathy Wiandt, 513-626-5225 (work) or 513-398-6035 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in DCF 5. If treatment by a physician is necessary, this treatment will be documented on DCF 6.

The following criteria will be used to determine the reporting time frame.

1. Any serious adverse events or adverse events requiring immediate medical attention will be reported to the Sponsor's Monitor immediately (night or day) by telephone.
2. Adverse events resulting in subject termination from the study will be reported during the immediate business day by telephone.
3. Adverse events that do not require discontinuation of test participation can be reported during the immediate business day or next business day by telephone.

4. In the event of a serious adverse reaction, not necessarily related to use of the test product, or in the event of a death from any cause, the Investigator must report the event to the Sponsor's Monitor and to the IRB as soon as possible..

B. Protocol Amendments

If it becomes necessary to modify this protocol, the modification will be documented by a protocol amendment signed by the investigator, a representative of the Sponsor and approved by the Institutional Review Board.. All amendments to the final protocol will be consecutively numbered and will describe any changes made and the rationale for making the changes.

C. Protocol Deviations

If a deviation from the final protocol occurs, it is the responsibility of the Investigator, or designee, to notify the Clinical Research Associate or designee. The Institutional Review Board will be notified within twenty-four hours of any deviation that poses additional risks to the subjects. The deviation and subsequent notification will be documented appropriately.

D. Study Monitoring

The Investigator will permit a representative of the Sponsor (usually the Clinical Research Associate) to visit the facility during the course of the study to monitor study progress. During the visit(s), the Investigator will permit the monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The study monitor will also be permitted to review and verify test articles, wash procedure, and any Investigator-generated or Sponsor-generated study documents. The monitor will document and discuss this visit with the Investigator, or his designee, including any problems that are to be resolved.

VI. Statistical Analyses

The investigator will be responsible for all statistical analyses. For the bag juice results, each subject's base sampling CFU's will be compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.05 will be considered statistically significant. Percent change for the test organism will be computed , if needed, by the following formula:

$$1 - \frac{\text{(geometric mean of the test CFU's)}}{\text{geometric mean of the baseline CFU's}} \times 100$$

Treatment comparisons will be made between the two wash treatments and the two wipe treatments. Treatment comparisons will be analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

VII. Investigator Responsibilities

A. Institutional Review Board (IRB) Review and Approval

Review by an IRB is required to conduct this study. A copy of the approval letter along with a list of the IRB members who acted on this protocol and a statement that the IRB is in compliance with current Good Clinical Practices (GCP) regulations will be provided to the Sponsor.

B. Subject Informed Consent

All subjects will be informed as to the type of study, the general nature of the products being tested, and any known or anticipated adverse reactions, which might result from participation. Each subject must provide the Investigator with written informed consent to serve as a participant in the study. Basic elements of informed consent are outlined in 21 CFR 50.25.

C. Final Report

The Sponsor will generate a final report of clinical results. The investigator will provide a detailed description of the adverse events and deviations from the protocol. The investigator will also include an accounting of the subjects screened, eliminated, enrolled and terminated. The Investigator will submit the legible copies of all data collection forms. The Sponsor may request one (1) copy of all data collection forms before the Investigator's report is ready for submission to the Sponsor.

D. Record Retention

The Investigator will retain all study records in accordance with the test facility's SOP's.

E. Confidentiality

The Investigator and employees of the test facility are obligated to keep any information confidential regarding any of the personal cleansing products and all aspects of the study, as subject to the terms and conditions of the Laboratory Services Agreement between the test facility and Sponsor.

VIII. References

1. *Annual Book of ASTM Standards*, Volume 11.04, ASTM Designation: E 1174-94, Standard Test Method for "Evaluation of Health Care Personnel Handwash Formulation".
2. Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule, 21 CFR Parts 333 and 369, *Federal Register*, Volume 59, No. 116, June 17, 1994.

IX. Attachments

The following Appendices, Data collection forms are included as attachments to the Final Protocol:

A	Written Informed Consent
B	Subject's Follow-up Instructions
C	Product Treatment
D	Schedule of Test Period Procedures
E	List of Representative Antibacterial/Antimicrobial Products
F	Microbiological Media and Methods

Data Collection Forms

1	Demographics/Dermatological/Medical History Form
2	Inclusion/Exclusion Form
3	Follow- up Visit
4	Microbiology Results
5	Adverse Event
6	Physician's Report Form

Source Documents

1	Treatment Phase (Baseline, Wash 1 and Wash 10)
2	Treatment Phase (Washes 2 through 9)

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Kathy Wiandt, B.A., Clinical Research Associate
Clinical Research and Biometrics Department

Date: 5/15/01

STATISTICIAN:

Jeanne C. Philippo,B.A., Statistician
Clinical Research and Biometrics Department

Date: 5/15/01

APPROVED BY:

Bruce Semple, M.D., Medical Director
Clinical Research and Biometrics Department

Date: 5/15/01

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Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator(s) for CRB-01-05-066-HB:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies including, but not limited to, those relating to Institutional Review Board (IRB), Informed Consent, and Good Clinical Practices.

I am aware that it is the responsibility of the Investigator to promptly report to the IRB all changes to the research activity and all unanticipated problems involving risk to human subjects. In addition, as Investigator, I am aware that a summary report must submitted to the IRB when the study is completed. These guidelines are in accordance with CFR 312.66. The Sponsor will be copied on all correspondence to and from the IRB.

Gayle K. Mulberry, M.S., Investigator — Date: 5-15-01

Kathleen A. Baxter, B.S., Sub-Investigator — Date: 5.15.01

Ann R. Brady, A.S., Sub-Investigator — Date: 5.15.01

Appendix A
HT-01-108592-11
CRB-01-05-066-HB

WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B
HT-01-108592-11
CRB-01-05-066-HB

SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Efficacy Evaluation Of Two Liquid Soap Products and Two Towelette Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia coli*". During this study, a quantity of bacteria (*E. coli)* was placed on the surface of both your hands. Although we do not expect you to have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your hands and wrists within four (4) to nine (9) days.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your hands and wrists daily. If you notice the appearance of any pimples, blisters or raised bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:00 am-5 p.m.) or at (513) 831-3354 after hours.

You are required to return to the test site for a follow-up visit. Your follow-up is scheduled for:

_____

Date Time

Thank you for your cooperation.

Appendix C

HT-01-108592-11
CRB-01-05-066-HB

PRODUCT TREATMENT PROCEDURE

Part I: *For subjects assigned to the Liquid Soap Product*

- **Water temperature should be maintained at 95 - 100° F.**
- **The temperature should be checked and recorded before each wash.**
- **The water pressure at each spigot to be used for the study should flow at 4 L/min.**
- **Subjects should remove all jewelry from hands and wrists prior to start of wash procedure.**

The following wash procedure will be performed by each subject:

1. Subjects will be instructed to wet their hands under the running water.
2. **2.0 mL of product** will be dispensed from a disposable syringe into the subjects' hands by a laboratory technician .
3. The technician will instruct the Subjects to lather all surfaces of their hands and wrists for **fifteen (15) seconds.**
4. Subjects will rinse their hands under running tap water for thirty (30) seconds.
5. A. For test washes #1 and #10, hands will not be dried.

   B. For test washes #2 through #9, subjects will dry their hands with paper towels.

   (Note: following the practice wash, subjects' hands will be disinfected and contaminated.)
6. Bags will be placed on the subjects' right and left hands for sampling after the first wash and after the tenth treatment. Sampling time will be approximately five (5) minutes following the wash with the test product.

OR

Part II: *For subjects assigned to the Towelette*

1. The technician will dispense the appropriate towelette test product into the subject's left hand using a gloved hand.
2. The subject will rub all surfaces of their right hand and wrist for fifteen (15) seconds while the technician instructs the subject to:
   - rub palm
   - rub back of hand
   - rub fingers and web areas between fingers
   - rub the tips of the fingers
3. The subject will transfer the wipe to their right hand.
4. The subject will rub their left hand and wrist for fifteen (15) seconds while the technician instructs the subjects to:
   - rub palm
   - rub back of hand
   - rub fingers and web areas between fingers
   - rub the tips of the fingers

Appendix D
HT-01-108592-11
CRB-01-05-066-HB

SCHEDULE OF TEST PERIOD PROCEDURES

1. **Practice treatment with Test Product:**

   For subjects assigned to the Liquid Soap Products

   - subjects wet hands under running tap water
   - dispense 2.0 mL of Baby San® into subjects' hands
   - subjects lather hands and wrists for fifteen (15) seconds
   - subjects rinse hands under running tap water for thirty (30) seconds
   - subjects dry hands with a paper towel

   For subjects assigned to the Towelette Products

   - towelette is placed in subjects' left hand
   - subject will rub all surfaces of their right hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips
   - subject transfers towelette to right hand
   - subject will rub all surfaces of their left hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips

2. **70% alcohol rinse**
   - squirt backs and palms of subjects' hands with 70% alcohol for 10 seconds
   - subjects rub alcohol over hands for 15 seconds
   - subjects rinse hands under running tap water for 15 seconds
   - subjects dry hands with paper towels

3. **Base contamination**
   - dispense 1.5 mL aliquot of bacterial suspension onto both subjects' hands
   - subjects rub aliquot over hands for 20 seconds
   - allow subjects' hands to air dry for approximately 30 seconds
   - repeat application 2 times
   - allow subjects' hands to air dry 1 minute after the last application

4. **Base sampling**
   - place bags on subject's right and left hands
   - dispense 75 mL stripping solution into each bag
   - secure bags
   - massage for 1 minute
   - sample each bag

5. **Water rinse**
   - subjects rinse hands with water for 30 seconds

6. **70% alcohol rinse**
   - perform as above

7. **Test contamination (prior to Test Product treatments 1 through 10)**
   - perform as above under base contamination

8. **Test Products Treatments (treatments 1 through 10)**
   - perform as described under practice treatment
   - for treatments #1 and #10, hands will not be dried prior to sampling
   - for treatments # 2 through #9 subjects will dry hands with paper towels

9. **Test sampling - Following Treatment 1**
   - perform as above under base sampling
   - subjects rinse hands with water for 30 seconds after the first test sampling

10. **Test sampling - Following Treatment 10**
    - place bag on of the subject's hands
    - dispense 75 mL stripping solution into the bag
    - secure bag
    - massage for 1 minute
    - sample bag

11. **Disinfection**
    - subject rinse hands for thirty (30) seconds
    - squirt subjects' hands with 2 mL of bland soap
    - subjects wash hands and wrists for approximately 30 seconds
    - subjects rinse hands and wrists for approximately 15 seconds
    - squirt subjects' hands with 5 mL of Hibiclens®
    - subjects wash hands and wrists for at least 60 seconds
    - subjects rinse hands and wrists for 15 seconds
    - squirt backs, palms and wrists of subjects' hands with 70% alcohol for 10 seconds
    - subjects rub alcohol over hands and wrists for 15 seconds
    - subjects' hands will be allowed to air dry

Appendix E
HT-01-108592-11
CRB-01-05-066-HB

LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Antibacterial Dishwashing Liquids

Dawn
Joy
Dial
Palmolive

Appendix F
HT-01-108592-11
CRB-01-05-066-HB

MICROBIOLOGICAL MEDIA AND METHODS

0.075M Phosphate Buffer Solution with Neutralizers

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80, 3 grams of lecithin, and 1.0 gram of Triton X-100. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ± 0.1 with 1 N HCl or 1 N NaOH. Dispense buffer in bottles so that after autoclaving the volume equals 75 ± 1 mL. Loosely cap bottles and sterilize in the autoclave at 121°C.

0.0375M Phosphate Buffer Solution with Neutralizers

Weigh 0.2 grams of KH_2PO_4, 5.05 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80 and 3 grams of lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ±0.1with 1 N HCl or 1 N NaOH. Dispense buffer in appropriate volumes. Loosely cap vessels and sterilize in the autoclave at
121°C.

MacConkey's Agar

Suspend 50 grams in 1 liter of distilled or deionized water. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45-50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Data Collection Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-IIB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male ☐ Female	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER	No	Yes	Don't Know
1. Psoriasis ?			
2. Eczema ?			
3. Skin Cancer ?			
4. Skin Allergies ? Please specify:			
5. Hives ?			

Does the Subject have any of the following (present and past)?

II. OTHER MEDICAL INFORMATION	No	Yes	Don't Know
1. Allergies.? Please specify.			
2. Hepatitis ?			
3. Heart and Vascular Disease?			
4. Liver Disease ?			
5. Kidney Disease ?			
6. Tuberculosis ?			
7. Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8. Cancer ?			
9. Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10. Organ transplant ?			
11. Any other condition not listed ? Please specify:			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION	No	Yes	Don't Know
1. Antibiotics, oral or systemic ?			
2. Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3. Heart Medication ?			
4. Insulin ?			
5. Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: _____/_____/_____ mm dd yy

Data Collection Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA

Check one YES	NO	Subject:
		1. Is ≥ 18 years ?
		2. Has signed informed consent?
		3. Is healthy as evidenced by responses on DCF 1 ?
		4. Has hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA

YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility ?
			2. Has participated in any type of hand or arm wash study within the past 7 days ?
			3. Has cuts, lesions, or other skin disorders on their hands or wrists ?
			4. Has soap, detergent, antibiotic and/or perfume allergies ?
			5. Has eczema or psoriasis on their hands or wrists ?
			6. Has used antibacterial/antimicrobial soaps, medicated lotions and creams and/or anti-dandruff shampoos within the last week?
			7. Has long (≥ 2 mm free edge) or artificial nails
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Data Collection 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Interviewer's Signature	Date: ___/___/___ mm dd yy
Investigator's Signature::	Date: ___/___/___ mm dd yy

Data Collection Form 3

FOLLOW-UP VISIT

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB		Follow-up	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date Subject Entered the Study:	Follow-up Visit Date :
___/___/___ mm dd yy	___/___/___ mm dd yy

Does the subject's hands have the presence of pimples, blisters, or raised itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection ?

YES NO If yes, complete below:

Clinical Observations: (Include date of onset and descriptions severity locations, etc.)

_____

_____

Comments: _____

_____

_____

_____

_____

_____

Has the subject had any health related issues since the treatment procedure?

YES NO If yes, complete below:

Comments: _____

_____

_____

_____

_____

_____

Investigator's Signature or designee	Date ___/___/___ mm dd yy

Data Collection Form 4
MICROBIOLOGICAL RESULTS

Study #	Hill Top Research, Inc.	Subject Intials	Permanent #
01-108592-11 CRB 01-04-051-HB		___/___/___ F M L	

BASE - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS			RIGHT HAND DILUTIONS		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
1						
2						

TEST #1 (after first treatment) - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS					RIGHT HAND DILUTIONS				
	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}
1										
2										
3										

TEST #2 (after tenth treatment) - Total # Organisms (CFU's) / mL of Sampling Solution

PLATE	LEFT HAND DILUTIONS					RIGHT HAND DILUTIONS				
	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-1}*	10^{-2}	10^{-3}	10^{-4}	10^{-5}
1										
2										
3										

Base Microbiologist(s):	**Date:**
Test Microbiologist(s):	**Date:**

*10^{-1} = 1 mL of sampling solution spread across three plates.

Data Collection Form 5

ADVERSE EVENT

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB			___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician

☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm dd yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
			/ /	
			/ /	
			/ /	

Investigator's Signature:	Recorded by:	Date ___/___/___ mm dd yy

Data Collection Form 6

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108592-11 CRB-01-05-066-HB			___ ___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature _____ Date

Source Document 1
TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108592-11 CRB-01-05-066-HB			

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Practice Wash	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	
Base Contamination Procedure	am/pm	☐ Yes / ☐ No	
Base Bacterial Sampling Procedure	am/pm	☐ Yes / ☐ No	
Base Decontamination	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #1	am/pm	☐ Yes / ☐ No	
Test Product Treatment #1	am/pm	☐ Yes ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #1 (after first treatment)	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #10	am/pm	☐ Yes / ☐ No	
Test Product Treatment #10	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #2 (after 10th treatment)	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	**Water Temp:** °F

Recorder's Signature:	Date: _____/_____/_____
Reviewer's Signature:	Date: _____/_____/_____

TREATMENT PHASE

Study #	Hill Top Research, Inc.	Permanent #'s
01-108592-11 CRB-01-05-066-HB		

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Test Contamination Procedure #2	am/pm	☐ Yes / ☐ No	
Test Product Treatment #2	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #3	am/pm	☐ Yes / ☐ No	
Test Product Treatment #3	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #4	am/pm	☐ Yes / ☐ No	
Test Product Treatment #4	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #5	am pm	☐ Yes / ☐ No	
Test Product Treatment #5	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #6	am/pm	☐ Yes / ☐ No	
Test Product Treatment #6	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #7	am/pm	☐ Yes / ☐ No	
Test Product Treatment #7	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #8	am/pm	☐ Yes / ☐ No	
Recorder's Signature:		Date: _____/_____/_____	
Reviewer's Signature:		Date: _____/_____/_____	

Source Document 2 (*continued*)
TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108592-11 CRB-01-05-066-HB			

Test Product Treatment #8	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #9	am/pm	☐ Yes / ☐ No	
Test Product Treatment #9	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Recorder's Signature:		Date: ____/____/____	
Reviewer's Signature:		Date: ____/____/____	

PILOT STUDY

RINSE OFF FORMULATION

SWH094-152, SW094-155

Clinical Study Report

CRA: Kathy Wiandt **Date:** May 23, 2001

Study Statistician: Jeanne Philippo **Retention Limit:** Until Superseded

Approved by: PBi 5/30/01

Subject: Results of Efficacy Evaluation of Two Handsoap Products in a Modified Healthcare Personnel Handwash Study Versus *Escherichia coli* – CRB-01-05-065-HB / HT# 01-108591-11.

Objective:

The objective of this study was to determine the ability of two antibacterial handsoap products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

Materials Tested: mf

Test Code	Test Material	Active Ingredient	Batch Number
A	Handwash Product	0% Salicylic Acid	SWH160-152
B	Handwash Product	2% Salicylic Acid	SWH160-155

Key Conclusions:

- After 1 wash, the 2.0% SA Hand Wash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0043).
- After 10 washes, the 2.0% SA Hand Wash had a significantly higher reduction in log counts versus the test placebo (p-value=0.0022).

The summary of the mean logs recovered and the log reductions achieved following the first and tenth washes were determined.

Table I –Summary of HCPHWT Log_{10} Bacterial Results

		Baseline	Log_{10}Counts – 1 Wash			Log_{10}Counts – 10 Washes		
Treatment	Sample Size	Mean	Mean	Change from Baseline	% Reduction	Mean	Change from Baseline	% Reduction
A-Handsoap 0% Salicylic Acid	6	7.63	5.21	2.42	99.6	5.44	2.19	99.4
B-Handsoap 2% Salicylic Acid	6	7.74	4.66	3.09	99.9	4.53	3.21	99.9

Study Summary:

Test Site: Hill Top Research, Miamiville, Ohio

Study Dates: May 8-14, 2001

Investigator: Gayle K. Mulberry, M.S.

Experimental Design: This was a randomized clinical study consisting of a one day test period and a single follow-up visit. Two test products were evaluated. Six subjects were used to evaluate each product.

Efficacy Measurements Taken: The subjects' hands were contaminated with a suspension of *E.coli*. Subjects' hands were contaminated eleven times and sampled three times using a plastic bag sampling procedure. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after one treatment with the assigned Test Product. After eleven contamination steps and ten treatments with the assigned Test Products the hands were sampled using the plastic bag sampling procedure.

Subject Demographics: Twelve male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions or creams and or antidandruff shampoos were enrolled into the study. Six subjects were used to evaluate one of two test products.

Overview: To become familiar with the wash procedure using a liquid hand soap, the subjects practiced the wipe procedure with Baby-san®. For the base count, subjects' hands were contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands were removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands were contaminated with *E. coli*. After completing the contamination step, the subjects performed the test product application procedure with the assigned Test Product. The subjects lathered their hands for fifteen seconds and rinsed their hands for thirty seconds. Approximately five minutes following the wipe procedure, the organisms on both of the subjects' hands were removed using a plastic bag sampling procedure. Approximately five minutes following the tenth treatment, the organisms on the subjects' hands were removed using a plastic bag sampling procedure

Samples of the subjects' sampling solutions were diluted, plated, and incubated. Following incubation, the numbers of colony forming units (CFU's) were enumerated. Antibacterial activity was determined by comparing the number of bacteria removed from the hands after one treatment with the assigned Test Product and ten treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

Data Analysis:

For the bag juice results, each subject's base sampling CFU's was compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 were considered statistically significant. Percent change for each organism was computed by the following formula:

$$1 - \left(\frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}}\right) \times 100$$

Treatment comparisons were analyzed by a Wilcoxon-Mann-Whitney Test using Exact methods.

Regulatory/Ethics Status:

This study was conducted in compliance with federal, state, and local regulations, guidelines, and standards including those related to Informed Consent and Good Clinical Practices as specified under 21 CRF 321.66.

Subject Accountability:

Twenty subjects were screened for the study. Twelve (12) subjects were screened, enrolled and completed this study. Five subjects met the study qualifications, but were excluded because they were extra subjects.

Two subjects were excluded because of open cuts on their hands. One subject was excluded because they were allergic to penicillin.

Adverse Events:

There were no adverse events in this study.

K Marriott
Clinical Research Associate

Jeanne C. Philippo
Statistician

HTR Study No.: 01-108591-11
Sponsor Study No.: CRB-01-05-065-HB

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of Hill Top Research, Inc. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records.

Data reviewed by:

Thomas Asplan 5-17-01

Thomas Asplan, A.A.S, B.S. Date
Auditor, Quality Assurance

CLINICAL STUDY PROTOCOL

Clinical Research & Biometrics Department
Sharon Woods Technical Center
Cincinnati, Ohio 45241

Title:	Efficacy Evaluation Of Two Liquid Soap Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*
Study Number:	CRB-01-05-065-HB HT# 01-108591-11
Issue Date:	5/4/01
Products Tested:	Antibacterial Handsoap Prototype Antibacterial Handsoap Prototype
Test Facility:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Microbiology Samples	The Procter and Gamble Company Miami Valley Laboratories
Principal Investigator:	Gayle Mulberry, M.S.
Sub-Investigators:	Kathleen A. Baxter, B.S. Ann R. Brady, A.S.
Test Sponsor:	The Procter & Gamble Co., Inc. Sharon Woods Technical Center 11520 Reed Hartman Highway Cincinnati, Ohio 45241

		work	home
Sponsor Toxicologist:	Candace Doepker, Ph.D	(513) 626-5536	
Sponsor Representative/CRA:	Kathy Wiandt, B.A.	(513) 626-5225	(513) 398-6035
Sponsor Statistician:	Jeanne Philippo, B.A.	(513) 626-5937	

Expected Study Start Date: May 8, 2001

Expected Study End Date: May 14, 2001

I. Study Objective and Background

A. Objective

The objective of the study is to determine the ability of a two antibacterial handwash product containing to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

B. Background

The skin microflora can be divided into two (2) groups, the resident flora and the transient flora. The resident flora includes organisms that are consistently present on the skin. The transient flora are the contaminating skin organisms resulting from contact with the environment. They comprise a wide variety of Gram positive and Gram negative species that can be responsible for the spread of infections and gastrointestinal diseases.

Since the benefits that result from washing with antibacterial soaps can not be easily measured under consumer use conditions, it is necessary to do controlled clinical studies to demonstrate their efficacy. This clinical study is a modification of an ASTM test method, "Evaluation of Health Care Personnel Handwash Formulation"(1) and reported in the Tentative Final Monograph for Health Care Antiseptic Drug Products(2). It is used to determine the ability of an antimicrobial handwashing agent, when used in a hand washing procedure, to reduce the transient microbial flora (contaminants). This study is designed to demonstrate the efficacy of two liquid handsoaps in reducing the numbers of a marker organism, *Escherichia coli* ATCC 11229 on the hands after a contamination and a single handwash and after ten handwashes. Efficacy is determined by comparing the numbers of marker organisms on the hands before and after using the test products.

C. Study Safety Statement

This testing meets the ethical requirements stipulated in the Sponsor's Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

II. Study Summary

A. Overview

This randomized clinical study will consist of a one day test period and a follow-up visit. Two (2) test products will be evaluated. Twelve (12) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and or antidandruff shampoos (Appendix E), will be enrolled into the study. Six (6) subjects will be used to evaluate each test product.

On the day of the study, the subjects will report to the clinical test facility. During this period, subjects' hands will be contaminated with a suspension of *E.coli*. Subjects' hands will be contaminated eleven (11) times and sampled three (3) times using a plastic bag sampling procedure. The first contamination and sampling will be for the determination of the base count. The second contamination and sampling will be for determination of the test count after one (1) treatment with the assigned Test Product. After eleven (11) contamination steps and ten (10) treatments with the assigned Test Products the hands will be sampled using the plastic bag sampling procedure

To become familiar with the wash procedure using the liquid hand soap, the subjects will begin the test procedure by first performing a practice wash with Baby-san®. For the base count, subjects will have their hands contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands will be contaminated with *E. coli*. After completing the contamination step, the subjects will perform the test product application procedure with the assigned

Test Product. Approximately five (5) minutes following the first procedure, the organisms on both of the subjects' hands will be removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure

Aliquots of the subjects' sampling solutions will be diluted, plated, and incubated. Following incubation, the number of colony forming units (CFU's) will be enumerated. Antibacterial activity is determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

B. Study Schedule

1. Subject Qualification and Enrollment

Prospective subjects will visit the test facility to be screened for their eligibility to participate in the study. Eligibility will be based upon information provided in the Demographics/Dermatological/ Medical History Form (DCF 1) and the Inclusion Exclusion Form (DCF 2); and completion of a written informed consent (Appendix A).

2. Test Period

Subjects continuing on the study will be assigned a permanent subject number. Subjects will be assigned to one of the two test products according to the study randomization.

The following outlines the schedule of procedures for the test day:

1. Subjects will perform a practice wash with Baby-san® (Appendix D).
2. Subjects will rinse their hands with 70% alcohol and rinse their hands under running tap water (Section G).
3. Subjects' hands will be contaminated (Section E).
4. Subjects' hands will be sampled for a base count (Section F).
5. Subjects will rinse their hands with water for 30 seconds (Section G).
6. Subjects will rinse their hands with 70% alcohol and rinse with tap water (Section G).
7. Subjects' hands will be contaminated (Section E).
8. Subjects will wash their hands following the wash procedure for the assigned Test Product (Section C, Appendix C).
9. Subjects' right and left hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the first wash with the assigned Test Product (Section F).
10. The hands will be rinsed for thirty seconds.
11. Subjects will perform steps 7 and 8 (above) a total of nine (9) more times at a minimum of five (5) minutes between each wash procedure.
12. The subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the tenth wash with the assigned Test Product (Section F).
13. Subjects' hands will be disinfected with a bland soap and water wash and Hibiclens® (4% chlorhexidine gluconate) wash and with a 70% alcohol rinse (Section G).

Note: A detailed scheduled of the above procedures can be found in Appendix D.

To ensure that any delayed adverse events, such as primary skin infections, are reported to the Study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study

Completion (Appendix B) before leaving the clinical site after they have completed the study. This sheet will instruct the subjects to examine their hands and wrists daily until the final scheduled visit for the presence of pimples, blisters, or raised, red itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection. Subjects, who notice such lesions, will be instructed to call the clinical test site. The subjects will return to the clinical test site within four (4) to nine (9) days after the study procedures have been completed to have their hands and wrists examined by a technician. The technician will complete DCF 3 for each subject on their follow-up visit.

C. Product Treatment Procedure

Subjects will wash their hands and wrists according to the procedure described in Product Treatment Procedure, Appendix C. In general the following should be noted:

a. Water temperature should be closely monitored and maintained at 95-100°F. The water temperature should be recorded on Source Document 1 or 2 before each wash.
b. Water pressure should be adjusted to a flow of 4 L/minute. This may be accomplished by placing a 2000 mL glass beaker or flask under each spigot to be used for subjects' hand washing. Allow the water to flow into the beaker. Adjust the water flow at each spigot accordingly, so that the beaker fills within thirty (30) seconds.
c. Subjects are to be closely supervised as they lather and wash their hands and wrists. The washes will be recorded on Source Documents 1 or 2.

D. Preparation of Bacterial Suspensions

A stock culture of *Escherichia coli*, ATCC 11229, will be prepared by transferring at least isolated (3) colony from an agar plate or slant aseptically to a tube containing sterile Trypticase Soy Broth (TSB). The inoculated broth will then be incubated for 24 ± 4 hours at 35 ± 2° C. At least three (3) additional 24 hour broth transfers will be made in tubes containing appropriate volumes TSB from this broth culture.

A 2-liter flask containing 1000 mL of TSB will be inoculated with 1.0 mL of the final 24 hour broth transfer. The flask will be incubated for 24 ± 4 hours at 35 ± 2° C. Prior to any withdrawal of culture, whether for hand contamination or for numbers assay, the suspension will be stirred or shaken. The suspension will be assayed for number of organisms at the beginning and end of the treatment period. A suspension will not be used for more than eight (8) hours.

E. Contamination

Note: Prior to contamination, subjects hands must be visibly dry. Also, care should be taken to ensure that the culture is evenly spread over both hands.

A total volume of 4.5 mL of the assigned bacterial suspension will be dispensed into the subjects' cupped hands in 1.5 mL increments. After each 1.5 mL aliquot is added, the suspension will be rubbed thoroughly over the surface of both hands, not going above the wrist and avoiding the nail beds. Each application and spreading should last approximately twenty (20) seconds. Between each aliquot the hands will be held away from the body and allowed to air dry for approximately thirty (30) seconds. Following the third 1.5 mL aliquot, the hands are allowed to air dry for approximately one (1) minute. A record of base and test contaminations will be documented on Source Document 1 or 2.

F. Bacterial Sampling Procedure

For removal of bacteria from the subjects' hands, loose fitting plastic bags with low bioburden will be placed on each subject's right and or left hands. A 75 mL aliquot of stripping solution [0.1% Triton X-100 in 0.075 M phosphate buffer, 1.0% polysorbate (Tween) 80, 0.3 % Lecithin, pH 7.9] will be aseptically added into each bag. The same solution will be used for the base counts and test counts.

The bag on each hand will be secured at the wrist with a child's size tourniquet and massaged for one (1) minute in a uniform manner by a lab technician. Aliquots of the solution will be aseptically obtained directly from the bag without touching the hands in the process and will be appropriately diluted in a sterile diluent with the appropriate neutralizer (for the test wash samples only). A record of base and test samplings will be documented on Source Document 1.

The solution samples for bacteria counts will be labeled by either an Investigator derived code or the actual subject's number so that the individuals who prepare the plates and count the CFU's are unaware of the sources of the sampling solution.

The solution will be aseptically placed in a sterile test tube. The test tube will be affixed with the subject number, baseline or post-treatment, and placed on ice for microbiological analysis. The sponsor will analyze the samples for microbiological content. The transfer of the microbial specimens will be recorded on Source Document 3.

G. Disinfection of Hands

After the baseline sampling, the subjects will rinse their hands for thirty (30) seconds under running tap water. The subjects' hands will be disinfected with a 70% alcohol wash. Subjects' hands will be squirted with 70% alcohol for approximately ten (10) seconds. Subjects will rub the alcohol over the surface of their hands and wrists for approximately fifteen (15) seconds. Subjects will rinse their hands and wrists under running tap water for approximately fifteen (15) seconds and dry their hands and wrists with paper towels.

After the final sampling is completed, the subject's hands will be washed with a bland soap (provided by the investigator) for approximately for thirty (30) seconds and rinsed for approximately fifteen (15) seconds. The subjects' hand will then be washed with Hibiclens® (4% chlorhexidine gluconate) for at least sixty (60) seconds. Subjects' hands and wrists will be rinsed with a 70% alcohol wash for ten (10) seconds. The subjects will rub the alcohol on all surfaces of their hands for fifteen (15) seconds and allow their hands to air dry.

A record of each disinfection procedure will be recorded on Source Document 1.

H. Plating and Incubation of the Organisms

Baseline specimens will be serially diluted in half-strength (0.0375 M) buffer (without Trtion X-100) in ten-fold dilutions to 10^{-3}, 10^{-4} and 10^{-5}. The diluted specimens will be plated using an automated plating system (Eddyjet system) onto MacConkey's agar. Post treatment specimens will be serially diluted in ten-fold dilutions to 10^{-1}, 10^{-2} 10^{-3} and 10^{-4}. Using an automated plating system (Eddyjet system), the undiluted and diluted specimens will be plated onto MacConkey's agar. The media for these analyses are shown in Appendix F.

Plated samples will be incubated aerobically for 18 - 24 hours at 35 $\pm$ 2°C. The plates will be analyzed using the Countermat®. The results will be reported as colonies per mL using the Countermat® software package.

The results will be recorded an electronic file created by the sponsor.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Data collection form (DCF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in DCF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or her designee.

A. Subject Inclusion Criteria

Subjects will be eligible for enrollment if they:

1. Are a male or female, over 18 years of age ;
2. Have signed a written informed consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/Dermatological/ Medical History Form (DCF 1);
4. Have hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders;
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

Subjects will not be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of arm or hand wash study within the past 7 days;
3. Have cuts, lesions, or other skin disorders on their hands or wrists;
4. Have soap, detergent, antibiotic, and/or perfume allergies;
5. Have eczema or psoriasis on their hands or arms;
6. Are using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos in the home within the last week (Appendix E);
7. Have excessively long or artificial nails (≥2 mm free edge) which would interfere with sampling;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator, would preclude participation.

D. Subject Number Assignment and Randomization

Upon entry into the study, each subject will be assigned a screening number beginning with 1001. Subjects will be assigned a permanent consecutive number, beginning with 001, as they are accepted into the study. This number will be used to identify the subject for the duration of the study.

IV. Study Material

A. Test Product

The test products will be sent by the Sponsor to the clinical site prior to study initiation. The test products will be identified with the appropriate label affixed to the outside of each container.

B. Shipping of Treatment Products and Other Study Supplies

The quantity of all treatment products and other study supplies, shipped to and returned from the clinical site, will be documented by the test site. The treatment products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc." with the facility's full

address and phone number);

3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator(s) will insure that all test products and study materials, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11520 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Kathy Wiandt

V. Other Study Documentation

A. Adverse Events

Should any unexpected or serious adverse event occur during the clinical study or as a result of test product or study procedures, the subject will be requested to return to the site to be examined by the investigator or designee. The Investigator will determine if the adverse event is likely to be associated with product treatment or the study procedures. The investigator or other qualified medical personnel will determine if the event warrants termination of participation and/or to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward L. Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Kathy Wiandt, 513-626-5225 (work) or 513-398-6035 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in DCF 4. If treatment by a physician is necessary, this treatment will be documented on DCF 5.

The following criteria will be used to determine the reporting time frame.

1. Any serious adverse events or adverse events requiring immediate medical attention will be reported to the Sponsor's Monitor immediately (night or day) by telephone.
2. Adverse events resulting in subject termination from the study will be reported during the immediate business day by telephone.
3. Adverse events that do not require discontinuation of test participation can be reported during the immediate business day or next business day by telephone.
4. In the event of a serious adverse reaction, not necessarily related to use of the test product, or in the event of a death from any cause, the Investigator must report the event to the Sponsor's Monitor.

B. Protocol Amendments

If it becomes necessary to modify this protocol, the modification will be documented by a protocol amendment signed by the investigator and a representative of the Sponsor. All amendments to the final protocol will be consecutively numbered and will describe any changes made and the rationale for making the changes.

C. Protocol Deviations

If a deviation from the final protocol occurs, it is the responsibility of the Investigator, or designee, to notify the Clinical Research Associate or designee. The deviation and subsequent notification will be documented appropriately.

D. Study Monitoring

The Investigator will permit a representative of the Sponsor (usually the Clinical Research Associate) to visit the facility during the course of the study to monitor study progress. During the visit(s), the Investigator will permit the monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The study monitor will also be permitted to review and verify test articles, wash procedure, and any Investigator-generated or Sponsor-generated study documents. The monitor will document and discuss this visit with the Investigator, or his designee, including any problems that are to be resolved.

VI. Statistical Analyses

The sponsor will be responsible for all statistical analyses. For the bag juice results, each subject's base sampling CFU's will be compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 will be considered statistically significant. Percent change for each organism will be computed , if needed, by the following formula:

$$1 - \frac{\text{(geometric mean of the test CFU's)}}{\text{geometric mean of the baseline CFU's}} \times 100$$

VII. Investigator Responsibilities

A. Subject Informed Consent

All subjects will be informed as to the type of study, the general nature of the products being tested, and any known or anticipated adverse reactions which might result from participation. Each subject must provide the Investigator with written informed consent to serve as a participant in the study. Basic elements of informed consent are outlined in 21 CFR 50.25.

B. Final Report

The Sponsor will generate a final report of clinical results. The investigator will provide a detailed description of the adverse events and deviations from the protocol. The investigator will also include an accounting of the subjects screened, eliminated, enrolled and terminated. The Investigator will submit the legible copies of all data collection forms. The Sponsor may request one (1) copy of all case report forms before the Investigator's report is ready for submission to the Sponsor.

C. Record Retention

The Investigator will retain all study records in accordance with the test facility's SOP's.

D. Confidentiality

The Investigator and employees of the test facility are obligated to keep any information confidential regarding any of the personal cleansing products and all aspects of the study, as subject to the terms and conditions of the Laboratory Services Agreement between the test facility and Sponsor.

VIII. References

1. *Annual Book of ASTM Standards*, Volume 11.04, ASTM Designation: E 1174-94, Standard Test Method for "Evaluation of Health Care Personnel Handwash Formulation".
2. Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule, 21 CFR Parts 333 and 369, *Federal Register*, Volume 59, No. 116, June 17, 1994.

IX. Attachments

The following Appendices, Data collection forms are included as attachments to the Final Protocol:

A Written Informed Consent
B Subject's Follow-up Instructions
C Product Treatment
D Schedule of Test Period Procedures
E List of Representative Antibacterial/Antimicrobial Products
F Microbiological Media and Methods

Data Collection Forms

1 Demographics/Dermatological/Medical History Form
2 Inclusion/Exclusion Form
3 Follow- up Visit
4 Adverse Event
5 Physician's Report Form

Source Documents

1 Treatment Phase (Baseline, Wash 1 and Wash 10)
2 Treatment Phase (Washes 2 through 9)
3 Shipping of Microbiological Specimens

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Kwiandt

Kathy Wiandt, B.A., Clinical Research Associate
Clinical Research and Biometrics Department

Date: 5/4/01

STATISTICIAN:

Jeanne C. Philippo

Jeanne C. Philippo,B.A., Statistician
Clinical Research and Biometrics Department

Date: 5/4/01

APPROVED BY:

Ward L. Billhimer

Ward L. Billhimer, M.S., Senior Scientist
Clinical Research and Biometrics Department

Date: 5/4/01

Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator(s) for CRB-01-05-064-HB:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies.

Gayle K. Mulberry, M.S., Investigator — Date: 5-7-01

Kathleen A. Baxter, B.S., Sub-Investigator — Date: 5.07.01

Ann R. Brady, A.S., Sub-Investigator — Date: 5.7.01

Appendix A
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WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B
HT-01-108591-11
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SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Efficacy Evaluation Of Two Liquid Soap Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*". During this study, a quantity of bacteria (*E. coli)* was placed on the surface of both your hands. Although we do not expect you to have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your hands and wrists within four (4) to nine (9) days.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your hands and wrists daily. If you notice the appearance of any pimples, blisters or raised bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:00 am-5 p.m.) or at (513) 831-3354 after hours.

You are required to return to the test site for a follow-up visit. Your follow-up is scheduled for:

_____

Date Time

Thank you for your cooperation.

Appendix C

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PRODUCT TREATMENT PROCEDURE

- **Water temperature should be maintained at 95 - 100° F.**
- **The temperature should be checked and recorded before each wash.**
- **The water pressure at each spigot to be used for the study should flow at 4 L/min.**
- **Subjects should remove all jewelry from hands and wrists prior to start of wash procedure.**

The following wash procedure will be performed by each subject:

1. Subjects will be instructed to wet their hands under the running water.
2. **2.0 mL of product** will be dispensed from a disposable syringe into the subjects' hands by a laboratory technician.
3. The technician will instruct the Subjects to lather all surfaces of their hands and wrists for **fifteen (15) seconds**.
4. Subjects will rinse their hands under running tap water for thirty (30) seconds.
5. A. For test washes #1 and #10, hands will not be dried.

   B. For test washes #2 through #9, subjects will dry their hands with paper towels.

   (Note: following the practice wash, subjects' hands will be disinfected and contaminated.)
6. Bags will be placed on the subjects' right and left hands for sampling after the first wash and after the tenth treatment. Sampling time will be approximately five (5) minutes following the wash with the test product.

Appendix D
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SCHEDULE OF TEST PERIOD PROCEDURES

1. **Practice treatment with Test Product:**
   - subjects wet hands under running tap water
   - dispense 2.0 mL of Baby San® into subjects' hands
   - subjects lather hands and wrists for fifteen (15) seconds
   - subjects rinse hands under running tap water for thirty (30) seconds
   - subjects dry hands with a paper towel
2. **70% alcohol rinse**
   - squirt backs and palms of subjects' hands with 70% alcohol for 10 seconds
   - subjects rub alcohol over hands for 15 seconds
   - subjects rinse hands under running tap water for 15 seconds
   - subjects dry hands with paper towels
3. **Base contamination**
   - dispense 1.5 mL aliquot of bacterial suspension onto both subjects' hands
   - subjects rub aliquot over hands for 20 seconds
   - allow subjects' hands to air dry for approximately 30 seconds
   - repeat application 2 times
   - allow subjects' hands to air dry 1 minute after the last application
4. **Base sampling**
   - place bags on subject's right and left hands
   - dispense 75 mL stripping solution into each bag
   - secure bags
   - massage for 1 minute
   - sample each bag
5. **Water rinse**
   - subjects rinse hands with water for 30 seconds
6. **70% alcohol rinse**
   - perform as above
7. **Test contamination (prior to Test Product treatments 1 through 10)**
   - perform as above under base contamination
8. **Test Products Treatments (treatments 1 through 10)**
   - perform as described under practice treatment
   - for treatments #1 and #10, hands will not be dried prior to sampling
   - for treatments # 2 through #9 subjects will dry hands with paper towels
9. **Test sampling - Following Treatment 1**
   - perform as above under base sampling
   - subjects rinse hands with water for 30 seconds after the first test sampling

10. Test sampling - Following Treatment 10

- place bag on of the subject's hands
- dispense 75 mL stripping solution into the bag
- secure bag
- massage for 1 minute
- sample bag

11. Disinfection

- subject rinse hands for thirty (30) seconds
- squirt subjects' hands with 2 mL of bland soap
- subjects wash hands and wrists for approximately 30 seconds
- subjects rinse hands and wrists for approximately 15 seconds
- squirt subjects' hands with 5 mL of Hibiclens®
- subjects wash hands and wrists for at least 60 seconds
- subjects rinse hands and wrists for 15 seconds
- squirt backs, palms and wrists of subjects' hands with 70% alcohol for 10 seconds
- subjects rub alcohol over hands and wrists for 15 seconds
- subjects' hands will be allowed to air dry

Appendix E
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LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Antibacterial Dishwashing Liquids

Dawn
Joy
Dial
Palmolive

Appendix F
HT-01-108591-11
CRB-01-05-065-HB

MICROBIOLOGICAL MEDIA AND METHODS

0.075M Phosphate Buffer Solution with Neutralizers

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80, 3 grams of lecithin, and 1.0 gram of Triton X-100. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ± 0.1 with 1 N HCl or 1 N NaOH. Dispense buffer in bottles so that after autoclaving the volume equals 75 ± 1 mL. Loosely cap bottles and sterilize in the autoclave at 121°C.

0.0375M Phosphate Buffer Solution with Neutralizers

Weigh 0.2 grams of KH_2PO_4, 5.05 grams of Na_2HPO_4, 10.0 grams of Polysorbate (Tween) 80 and 3 grams of lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ±0.1with 1 N HCl or 1 N NaOH. Dispense buffer in appropriate volumes. Loosely cap vessels and sterilize in the autoclave at 121°C.

MacConkey's Agar

Suspend 50 grams in 1 liter of distilled or deionized water. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45-50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Data Collection Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108591-11 CRB-01-05-065-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male ☐ Female	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER	No	Yes	Don't Know
1. Psoriasis ?			
2. Eczema ?			
3. Skin Cancer ?			
4. Skin Allergies ? Please specify:			
5. Hives ?			

Does the Subject have any of the following (present and past)?

II. OTHER MEDICAL INFORMATION	No	Yes	Don't Know
1. Allergies.? Please specify.			
2. Hepatitis ?			
3. Heart and Vascular Disease?			
4. Liver Disease ?			
5. Kidney Disease ?			
6. Tuberculosis ?			
7. Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8. Cancer ?			
9. Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10. Organ transplant ?			
11. Any other condition not listed ? Please specify:			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION	No	Yes	Don't Know
1. Antibiotics, oral or systemic ?			
2. Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3. Heart Medication ?			
4. Insulin ?			
5. Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: _____/_____/_____ mm dd yy

Data Collection Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108591-11 CRB-01-05-065-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA

Check one YES	NO	Subject:
		1. Is ≥ 18 years ?
		2. Has signed informed consent?
		3. Is healthy as evidenced by responses on DCF 1 ?
		4. Has hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA

YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility ?
			2. Has participated in any type of hand or arm wash study within the past 7 days ?
			3. Has cuts, lesions, or other skin disorders on their hands or wrists ?
			4. Has soap, detergent, antibiotic and/or perfume allergies ?
			5. Has eczema or psoriasis on their hands or wrists ?
			6. Has used antibacterial/antimicrobial soaps, medicated lotions and creams and/or anti-dandruff shampoos within the last week?
			7. Has long (≥ 2 mm free edge) or artificial nails
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Data Collection 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Interviewer's Signature	Date: ___/___/___ mm dd yy
Investigator's Signature::	Date: ___/___/___ mm dd yy

TREATMENT PHASE

Study #	Hill Top Research, Inc.	Permanent #'s
01-108591-11 CRB-01-05-065-HB		

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Test Contamination Procedure #2	am/pm	☐ Yes / ☐ No	
Test Product Treatment #2	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #3	am/pm	☐ Yes / ☐ No	
Test Product Treatment #3	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #4	am/pm	☐ Yes / ☐ No	
Test Product Treatment #4	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #5	am/pm	☐ Yes / ☐ No	
Test Product Treatment #5	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #6	am/pm	☐ Yes / ☐ No	
Test Product Treatment #6	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #7	am/pm	☐ Yes / ☐ No	
Test Product Treatment #7	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #8	am/pm	☐ Yes / ☐ No	
Recorder's Signature:		Date: ____/____/____	
Reviewer's Signature:		Date: ____/____/____	

Source Document 2 (*continued*)

TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108591-11 CRB-01-05-065-HB			

Test Product Treatment #8	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #9	am/pm	☐ Yes / ☐ No	
Test Product Treatment #9	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Recorder's Signature:		Date: ____/____/____	
Reviewer's Signature:		Date: ____/____/____	

Source Document 1
TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108591-11 CRB-01-05-065-HB			

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Practice Wash	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	
Base Contamination Procedure	am/pm	☐ Yes / ☐ No	
Base Bacterial Sampling Procedure	am/pm	☐ Yes / ☐ No	
Base Decontamination	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #1	am/pm	☐ Yes / ☐ No	
Test Product Treatment #1	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #1 (after first treatment)	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #10	am/pm	☐ Yes / ☐ No	
Test Product Treatment #10	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #2 (after 10th treatment)	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	**Water Temp:** °F

Recorder's Signature:	Date: _____/_____/_____
Reviewer's Signature:	Date: _____/_____/_____

Data Collection Form 3

FOLLOW-UP VISIT

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108591-11 CRB-01-05-065-HB		Follow-up	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date Subject Entered the Study:	Follow-up Visit Date :
_____/_____/_____ mm dd yy	_____/_____/_____ mm dd yy

Does the subject's hands have the presence of pimples, blisters, or raised itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection ?

YES NO If yes, complete below:

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Comments: _____

_____

_____

_____

_____

_____

Has the subject had any health related issues since the treatment procedure?

YES NO If yes, complete below:

Comments: _____

_____

_____

_____

_____

_____

Investigator's Signature or designee	Date _____/_____/_____ mm dd yy

Data Collection Form 4

ADVERSE EVENT

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108591-11 CRB-01-05-065-HB			___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician ☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm / dd / yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	

Investigator's Signature:	Recorded by:	Date ___/___/___ mm dd yy

Data Collection Form 5

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108591-11 CRB-01-05-065-HB			___ ___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions severity locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature

_____ Date

Study Title: "Efficacy Evaluation of Two Liquid Soap Products In a Modified Health Care Personnel Handwash Study Versus *Escherichia coli*"

CONSENT FORM

INTRODUCTION: You are being asked to take part in a research study. Before you give your consent to be a subject, it is important that you take enough time to read and understand what your participation would involve. In preparing this consent form, it has been necessary to use some technical language. Please ask questions if there is anything you do not understand.

You will be given a signed copy of this consent form and any other necessary written information prior to the start of the study.

PURPOSE: The purpose of this research study is to determine the effectiveness of two liquid soap products containing an antibacterial ingredient against bacteria found on the skin. Approximately twenty (20) people at least 18 years of age will be screened as potential subjects in this study. At least twelve (12) subjects are expected to complete the two-visit study.

TEST ARTICLES: You will be assigned 1 of the two antibacterial liquid soap products. The liquid soap products are experimental.

STUDY PROCEDURES: Prior to enrollment in the test, you will be asked to complete a brief medical history questionnaire and another form to determine your eligibility for the study. Your hands and wrists will be checked for visible cuts, scratches or rashes on them. It is possible that you may not be able to participate based on your answers to these questions or the condition of the skin on your hands and wrists.

If you are selected to participate in this study, you will be instructed to perform a practice treatment with a liquid soap product. Then, your hands will be rinsed with alcohol, rubbed for about 15 seconds and rinsed in tap water for 15 seconds followed by drying with paper towels. Afterwards, your hands will be contaminated with a watery liquid containing relatively non-harmful bacteria (*Escherichia coli*). This liquid containing the bacteria will be spread over the surfaces of the hands, and the hands will be allowed to air dry. Following air drying, the hands will be sampled. Sampling is accomplished by having you place your hands into large plastic bags to which will be added a mild soap-like solution. A laboratory technician will massage each bagged hand for one minute. The hands will be removed from the bags and the solution from each bag will be tested to determine the number of test bacteria added to the hands. Following this baseline sampling, the hands will be rinsed for 30 seconds with tap water, rinsed with 70% alcohol and water, then dried with paper towels. Then the hands will be contaminated as above and treated with the assigned test material, 1

of the 2 liquid soap products following specific directions. After the treatment with the liquid soap product, your hands will be sampled as above about 4-5 minutes after the first treatment is completed to determine the number of bacteria removed or killed by treatment. Your hands will be contaminated and treated 10 times. After the 10th treatment, sampling will be repeated. Following each sampling, your hands will be rinsed with tap water. After the final sampling your hands will then be washed with a plain soap followed by a wash with Hibiclens®, an antimicrobial soap, and rinsed with alcohol prior to leaving the lab.

After completing the treatment visit and until your follow-up visit, you will need to check the skin on your hands each day for any pimples, bumps or rashes. Within four to nine days after you have completed treatment, you will be required to return to the lab for a follow-up visit. Your hands will be checked for infection by a technician trained in observing infection.

FEMALES OF CHILDBEARING POTENTIAL: You may not participate in this study if you are pregnant or nursing. As part of giving your consent you must agree to have a urine pregnancy test at the start of the study.

RISKS: The risks associated with this test are primarily related to infection with the test bacteria. For healthy persons, the possibility of a skin infection exists; however, this possibility is remote because, (1) test bacteria are applied only to healthy or uninjured skin, and (2) the skin is cleansed with antibacterial products following contact with the test bacteria. Your hands may also show a "reaction." A "reaction" could be pimples, blisters or raised bumps surrounded by redness and/or swelling. It is unlikely, but possible, that a rash could develop.

No risks to you as a study participant, other than those described above as "reactions," are anticipated during the study. Reactions are usually due to irritation, although an allergic reaction might occur. If you become allergic, it is possible that future exposures to the same ingredient may cause a skin reaction. If this occurs, you will be provided with information to minimize the chance for future exposures.

You may experience risks or side effects that are not known at this time. You will be informed in a timely manner if new information becomes available that may influence your willingness to continue in this study.

BENEFITS: You will not benefit from the application of test product but the study results may allow a new or improved product to be marketed.

ALTERNATIVE PROCEDURES/TREATMENTS: Because you are not being treated for a medical condition, alternative treatments do not apply to this study.

CONFIDENTIALITY: Information concerning you that is obtained in connection with this study will be kept confidential by Hill Top Research, except that the sponsoring company whose product is being tested will receive a copy of the study records. The records will be coded to protect your identity. In addition, government regulatory agencies, including the U.S. Food and Drug Administration (FDA), may inspect the records of the study. Information obtained in the study may be used for medical or scientific publication, but your identity will remain confidential.

MEDICAL TREATMENT: If in the course of this study you experience illness, discomfort or injury that appears to be a result of the study, Hill Top Research will provide you with medical care at no cost to you. Providing such medical care is not an admission of legal responsibility. If such illness, discomfort or injury does occur, ask any staff member to arrange a meeting for you with the appropriate personnel.

In certain cases of illness or injury resulting from this study, workers' compensation coverage may be available. In accordance with Ohio law, Hill Top Research has secured workers' compensation coverage for participants in its studies and tests, and has paid and will pay appropriate premiums into the State Insurance Fund on behalf of such participants.

WHO TO CONTACT: If you have any questions about this study or in case of an emergency, contact Emilie, Study Coordinator at 513-831-3114, ext. 2324 during business hours (M-F, 8:00 A.M. - 5:00 P.M.) or Ann Brady, Study Manager at 513-831-3354 after hours.

VOLUNTARY PARTICIPATION/WITHDRAWAL: Your participation in this research study is strictly voluntary. You may refuse to participate or may discontinue participation at any time during the study without penalty or loss of benefits to which you are otherwise entitled.

If you agree to participate in this study, you are also agreeing to provide Hill Top Research with accurate information and to follow study instructions as given to you. If you fail to comply with study procedures, your participation may be terminated.

Your participation in the study may be discontinued at any time without your consent by the Investigator, the FDA, or the sponsoring company.

COMPENSATION: You will be paid $55.00 for the completion of this study. You will be compensated according to the following schedule:

If you do not qualify	Visit 1	you will receive	$10.00
If you qualify but are eliminated as an extra subject	Visit 1	you will receive	$15.00
If you complete	Visit 1	you will receive	$30.00
If you complete	Visit 2	you will receive	$55.00

Payments will be made at the end of the study.

There are no anticipated expenses to you for participating in this study. All test related materials will be provided at no cost to you.

CONSENT TO PARTICIPATE

I know that my participation in this study is voluntary and that I have the right to refuse to participate. I know that I may withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled. If I withdraw or am dismissed for failure to obey rules or follow directions, I understand I will only be paid for the portion of the study that I have completed. If, in the judgment of the Investigator, it is best to discontinue my participation in the study for other reasons, I will be paid either in full or for that portion of the study already completed.

If I am a female of childbearing potential, I am not currently pregnant or nursing an infant. I am using an adequate means of birth control and, if I become pregnant or believe I have become pregnant, I will notify the Investigator immediately.

CONSENT: I have read all of the above information and have been given an opportunity to ask questions about this study. Answers to such questions (if any) were satisfactory. I am eighteen years of age or older and freely and without reservation give my consent to serve as a subject in this study. By signing this form, I have not given up any of my legal rights as a research subject.

_____

Subject's Name Printed: First Middle Initial Last

_____

Subject's Signature Date

_____

Signature of Person Conducting Consent Discussion Date

SUBJECT SCREEN NO. _____
SUBJECT NO. _____

PILOT STUDY

NON-RINSE OFF FORMULATION

SWH094-136, SWH094-137

Clinical Study Report

CRA: Kathy Wiandt **Date:** May 22, 2001

Study Statistician: Jeanne Philippo **Retention Limit:** Until Superseded

Approved by: 9R 5/30/01

Subject: Results of Efficacy Evaluation of Three Handwipe Products in a Modified Healthcare Personnel Handwash Study Versus *Escherichia coli* – CRB-01-04-063-HB / HT# 01-108589-11.

Objective:

The objective of this study was to determine the ability of three antibacterial handwipe products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

Materials Tested:

Test Code	Test Material	Active Ingredient	Batch Number
A	Handwipe Product	1% Salicylic Acid	SWH94-136
B	Handwipe Product	0% Salicylic Acid	SWH94-137
C	Handwipe Product	2% Salicylic Acid	SWH94-138

Key Conclusions:

The purpose of this test was to screen antibacterial handwipe prototypes. The base size per product tested was small and therefore no statistical differences were determined between the products.

The summary of the mean logs recovered and the log reductions achieved following the first and tenth washes were determined.

Table I –Summary of HCPHWT Log_{10} Bacterial Results

		Baseline	Log_{10}Counts – 1 Wash			Log_{10}Counts – 10 Washes		
Treatment	Sample Size	Mean	Mean	Change from Baseline	% Reduction	Mean	Change from Baseline	% Reduction
A-Handwipe 1% Salicylic Acid	4	7.43	5.54	1.89	98.7	4.05	3.38	>99.9
B-Handwipe 0% Salicylic Acid	4	6.78	5.35	1.43	96.3	4.34	2.44	99.6
C-Handwipe 2% Salicylic Acid	4	7.45	5.43	2.01	99.0	4.44	3.01	99.9

Attached are the statistical analysis tables for the study.

Study Summary:

Test Site: Hill Top Research, Miamiville, Ohio

Study Dates: April 20-24, 2001

Investigator: Gayle K. Mulberry, M.S.

Experimental Design: This was a randomized clinical study consisting of a one day test period and a single follow-up visit. Three test products were evaluated. Four subjects were used to evaluate each product.

Efficacy Measurements Taken: The subjects' hands were contaminated with a suspension of *E.coli*. Subjects' hands were contaminated eleven (11) times and sampled three times using a plastic bag sampling procedure. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after one treatment with the assigned Test Product. After eleven contamination steps and ten treatments with the assigned Test Products the hands were sampled using the plastic bag sampling procedure.

Subject Demographics: Twelve (12) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions or creams and or antidandruff shampoos were enrolled into the study. Four (4) subjects were used to evaluate one of three test products.

Overview: To become familiar with the wipe procedure using non-medicated hand wipe, the subjects practiced the wipe procedure with Nice 'n' Clean®. For the base count, subjects' hands were contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands were removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands were contaminated with *E. coli*. After completing the contamination step, the subjects performed the test product application procedure with the assigned Test Product. The subjects wiped each of their hands for fifteen (15) seconds. Approximately five (5) minutes following the wipe procedure, the organisms on both of the subjects' hands were removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands were removed using a plastic bag sampling procedure

Samples of the subjects' sampling solutions were diluted, plated, and incubated. Following incubation, the numbers of colony forming units (CFU's) were enumerated. Antibacterial activity was determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

Data Analysis:

For the bag juice results, each subject's base sampling CFU's was compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 were considered statistically significant. Percent change for each organism was computed by the following formula:

$$1 - \left(\frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}} \right) \times 100$$

Regulatory/Ethics Status:

This study was conducted in compliance with federal, state, and local regulations, guidelines, and standards including those related to Informed Consent and Good Clinical Practices as specified under 21 CRF 321.66.

Subject Accountability:

Eighteen (18) subjects were screened for the study. Twelve (12) subjects were screened, enrolled and completed this study. Four (4) subjects met the study qualifications, but were excluded because they were extra subjects. Two (2) subjects were excluded because of open cuts on their hands.

Adverse Events:

There were no adverse events in this study.

K Wrandt
Clinical Research Associate

Jeanne C. Philippo
Statistician

			Baseline Log10(Count)			Final Log10(Count)		
Wash	Treatment	Sample Size	Mean	Median	Std.Error	Mean	Median	Std.Error
1	A:	4	7.43	7.41	0.053	5.54	5.54	0.140
	B:	4	6.78	6.68	0.229	5.35	5.44	0.284
	C:	4	7.45	7.46	0.048	5.43	5.40	0.069
10	A:	4	7.43	7.41	0.053	4.05	4.08	0.341
	B:	4	6.78	6.68	0.229	4.34	4.31	0.227
	C:	4	7.45	7.46	0.048	4.44	4.98	0.660

			Change in Log10(Count)				
Wash	Treatment	Sample Size	Mean	Median	Std.Error	P-Value	Percent Reduction
1	A:	4	1.89	1.91	0.133	0.1250	98.7
	B:	4	1.43	1.46	0.125	0.1250	96.3
	C:	4	2.01	2.11	0.108	0.1250	99.0
10	A:	4	3.38	3.37	0.344	0.1250	>99.9
	B:	4	2.44	2.46	0.055	0.1250	99.6
	C:	4	3.01	2.41	0.662	0.1250	99.9

Summary of HCPHWT Log10 Bacterial Results								
			Log10 Counts - 1 Wash			Log10 Counts - 10 Washes		
Treatment	Sample Size	Baseline Mean	Mean	Change from Baseline	Percent Reduction	Mean	Change from Baseline	Percent Reduction
A:	4	7.43	5.54	1.89	98.7	4.05	3.38	>99.9
B:	4	6.78	5.35	1.43	96.3	4.34	2.44	99.6
C:	4	7.45	5.43	2.01	99.0	4.44	3.01	99.9

HTR Study No.: 01-108589-11
Sponsor Study No.: CRB-01-04-063-HB

QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of Hill Top Research, Inc. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records.

Data reviewed by:

Richard D. Pendleton 5/2/01

Richard D. Pendleton, B.S. Date
Auditor, Quality Assurance

CLINICAL STUDY PROTOCOL

Clinical Research & Biometrics Department
Sharon Woods Technical Center
Cincinnati, Ohio 45241

Title:	Efficacy Evaluation Of Three Handwipe Products In A Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*
Study Number:	CRB-01-04-063-HB / HT# 01-108589-11
Issue Date:	4/18/01
Products Tested:	Antibacterial Handwipe Prototype Antibacterial Handwipe Prototype Antibacterial Handwipe Prototype
Test Facility:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Microbiology Samples	The Procter and Gamble Company Miami Valley Laboratories
Principal Investigator:	Gayle Mulberry, M.S.
Sub-Investigators:	Kathleen A. Baxter, B.S. Ann R. Brady, A.S.
Test Sponsor:	The Procter & Gamble Co., Inc. Sharon Woods Technical Center 11520 Reed Hartman Highway Cincinnati, Ohio 45241

		work	home
Sponsor Toxicologist:	Candace Doepker, Ph.D.	(513) 626-5536	
Sponsor Representative/CRA:	Kathy Wiandt, B.A.	(513) 626-5225	(513) 398-6035
Sponsor Statistician:	Jeanne Philippo, B.A.	(513) 626-5937	
Expected Study Start Date:	April 20, 2001		
Expected Study End Date:	April 24, 2001		

I. Study Objective and Background

A. Objective

The objective of the study is to determine the ability of a three antibacterial handwipe products to significantly reduce transient microbial flora (*Escherichia coli* 11229) on the hands after a single treatment and after ten (10) treatments.

B. Background

The skin microflora can be divided into two (2) groups, the resident flora and the transient flora. The resident flora includes organisms that are consistently present on the skin. The transient flora are the contaminating skin organisms resulting from contact with the environment. They comprise a wide variety of Gram positive and Gram negative species that can be responsible for the spread of infections and gastrointestinal diseases.

Since the benefits that result from washing with antibacterial products can not be easily measured under consumer use conditions, it is necessary to do controlled clinical studies to demonstrate their efficacy. This clinical study is a modification of an ASTM test method, "Evaluation of Health Care Personnel Handwash Formulation"[1] and reported in the Tentative Final Monograph for Health Care Antiseptic Drug Products[2]. It is used to determine the ability of an antimicrobial handwashing agent, when used in a hand washing procedure, to reduce the transient microbial flora (contaminants). This study is designed to demonstrate the efficacy of three towelette products in reducing the numbers of a marker organism, *Escherichia coli* ATCC 11229 on the hands after a contamination and a single treatment and after ten treatments. Efficacy is determined by comparing the numbers of marker organisms on the hands before and after using the test products.

C. Study Safety Statement

This testing meets the ethical requirements stipulated in the Sponsor's Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

II. Study Summary

A. Overview

This randomized clinical study will consist of a one day test period and a follow-up visit. Three (3) test products will be evaluated. Twelve (12) male and female subjects, ≥ 18 years old, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and or antidandruff shampoos (Appendix D), will be enrolled into the study. Four (4) subjects will be used to evaluate each test product.

On the day of the study, the subjects will report to the clinical test facility. During this period, subjects' hands will be contaminated with a suspension of *E.coli*. Subjects' hands will be contaminated eleven (11) times and sampled three (3) times using a plastic bag sampling procedure. The first contamination and sampling will be for the determination of the base count. The second contamination and sampling will be for determination of the test count after one (1) treatment with the assigned Test Product. After eleven (11) contamination steps and ten (10) treatments with the assigned Test Products the hands will be sampled using the plastic bag sampling procedure

To become familiar with the wipe procedure using the towelette product, subjects will begin the test procedure by first performing a practice wipe with Nice 'n' Clean®. For the base count, subjects will have their hands contaminated with *E. coli*. Immediately following the contamination step, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure.

Prior to each treatment wash, subjects' hands will be contaminated with *E. coli*. After completing the contamination step, the subjects will perform the test product application procedure with the assigned

Test Product. Approximately five (5) minutes following the first procedure, the organisms on both of the subjects' hands will be removed using a plastic bag sampling procedure. Approximately five (5) minutes following the tenth treatment, the organisms on the subjects' hands will be removed using a plastic bag sampling procedure

Aliquots of the subjects' sampling solutions will be diluted, plated, and incubated. Following incubation, the number of colony forming units (CFU's) will be enumerated. Antibacterial activity is determined by comparing the number of bacteria removed from the hands after one (1) treatment with the assigned Test Product and ten (10) treatments with the assigned Test Product to the number of bacteria removed from unwashed hands.

B. Study Schedule

1. Subject Qualification and Enrollment

Prospective subjects will visit the test facility to be screened for their eligibility to participate in the study. Eligibility will be based upon information provided in the Demographics/Dermatological/ Medical History Form (DCF 1) and the Inclusion/Exclusion Form (DCF 2); and completion of a written informed consent (Appendix A).

2. Test Period

Subjects continuing on the study will be assigned a permanent subject number. Subjects will be assigned to one of the three test products according to the study randomization.

The following outlines the schedule of procedures for the test day:

1. Subjects will perform a practice wipe with Nice 'n' Clean ®.
2. Subjects will rinse their hands with 70% alcohol and rinse their hands under running tap water (Section G).
3. Subjects' hands will be contaminated (Section E).
4. Subjects' hands will be sampled for a base count (Section F).
5. Subjects will rinse their hands with water for 30 seconds (Section G).
6. Subjects will rinse their hands with 70% alcohol and rinse with tap water (Section G).
7. Subjects' hands will be contaminated (Section E).
8. Subjects will wipe their hands following the wipe procedure for the assigned Test Product (Section C).
9. Subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the first wipe with the assigned Test Product (Section F).
10. The hands will be rinsed for thirty seconds.
11. Subjects will perform steps 7 and 8 (above) a total of nine (9) more times at a minimum of five (5) minutes between each wash procedure.
12. The subjects' hands will be sampled for a treatment value four (4) minutes and thirty (30) seconds ± thirty (30) seconds after the tenth wipe with the assigned Test Product (Section F).
13. Subjects' hands will be disinfected bland soap and water wash and Hibiclens® (4% chlorhexidine gluconate) wash and with a 70% alcohol rinse (Section G).

Note: A detailed scheduled of the above procedures can be found in Appendix C.

To ensure that any delayed adverse events, such as primary skin infections, are reported to the Study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study Completion (Appendix B) before leaving the clinical site after they have completed the study. This

sheet will instruct the subjects to examine their hands and wrists daily until the final scheduled visit for the presence of pimples, blisters, or raised, red itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection. Subjects, who notice such lesions, will be instructed to call the clinical test site. The subjects will return to the clinical test site within four (4) to nine (9) days after the study procedures have been completed to have their hands and wrists examined by a technician. The technician will complete DCF 3 for each subject on their follow-up visit.

C. Product Treatment Procedure

Subjects will wipe their hands and wrists according to the procedure below. A record of the product treatment procedure will be documented on Source Documents 1 or 2

1. The technician will dispense the Test Product into the subject's left hand using a gloved hand.
2. The subject will rub all surfaces of their right hand and wrist for fifteen (15) seconds while the technician instructs the subject to:
    - rub palm
    - rub back of hand
    - rub the wrist
    - rub fingers and web areas between fingers
    - rub the tips of the fingers
3. The subject will transfer the wipe to their right hand.
4. The subject will rub all surfaces of their left hand and wrist for fifteen (15) seconds while the technician instructs the subject to:
    - rub palm
    - rub back of hand
    - rub the wrist
    - rub fingers and web areas between fingers
    - rub the tips of the fingers

D. Preparation of Bacterial Suspensions

A stock culture of *Escherichia coli*, ATCC 11229, will be prepared by transferring one (1) colony from an agar plate or slant aseptically to a tube containing sterile Trypticase Soy Broth (TSB). The inoculated broth will then be incubated for 24 ± 4 hours at 35 ± 2° C. At least three (3) additional 24 hour broth transfers will be made in tubes containing appropriate volumes TSB from this broth culture.

A 2-liter flask containing 1000 mL of TSB will be inoculated with 1.0 mL of the final 24 hour broth transfer. The flask will be incubated for 24 ± 4 hours at 35 ± 2° C. Prior to any withdrawal of culture, whether for hand contamination or for numbers assay, the suspension will be stirred or shaken. The suspension will be assayed for number of organisms at the beginning and end of the treatment period. A suspension will not be used for more than eight (8) hours.

E. Contamination

Note: Prior to contamination, subjects hands must be visibly dry. Also, care should be taken to ensure that the culture is evenly spread over both hands.

A total volume of 4.5 mL of the assigned bacterial suspension will be dispensed into the subjects' cupped hands in 1.5 mL increments. After each 1.5 mL aliquot is added, the suspension will be rubbed thoroughly over the surface of both hands, not going above the wrist and avoiding the nail beds. Each application and spreading should last approximately twenty (20) seconds. Between each aliquot the hands will be held away from the body and allowed to air dry for approximately thirty (30) seconds.

Following the third 1.5 mL aliquot, the hands are allowed to air dry for approximately one (1) minute. A record of base and test contaminations will be documented on Source Document 1 or 2.

F. Bacterial Sampling Procedure

For removal of bacteria from the subjects' hands, loose fitting plastic bags with low bioburden will be placed on each subject's right and/or left hands. A 75 mL aliquot of stripping solution [0.1% Triton X-100 in 0.075 M phosphate buffer, 0.5% polysorbate (Tween) 80, 0.07% Lecithin, pH 7.9] will be aseptically added into each bag. The same solution will be used for the base counts and test counts.

The bag on each hand will be secured at the wrist with a child's size tourniquet and massaged for one (1) minute in a uniform manner by a lab technician. Aliquots of the solution will be aseptically obtained directly from the bag without touching the hands in the process and will be appropriately diluted in a sterile diluent with the appropriate neutralizer (for the test wash samples only). A record of base and test samplings will be documented on Source Document 1.

The solution samples for bacteria counts will be labeled by either an Investigator derived code or the actual subject's number so that the individuals who prepare the plates and count the CFU's are unaware of the sources of the sampling solution.

The solution will be aseptically placed in a sterile test tube. The test tube will be affixed with the subject number, baseline or post-treatment, and placed on ice for microbiological analysis. The sponsor will analyze the samples for microbiological content. The transfer of the microbial specimens will be recorded on Source Document 3.

G. Disinfection of Hands

After the baseline sampling, the subjects will rinse their hands for thirty (30) seconds under running tap water. The subjects' hands will be disinfected with a 70% alcohol wash. Subjects' hands will be squirted with 70% alcohol for approximately ten (10) seconds. Subjects will rub the alcohol over the surface of their hands and wrists for approximately fifteen (15) seconds. Subjects will rinse their hands and wrists under running tap water for approximately fifteen (15) seconds and dry their hands and wrists with paper towels.

After the final sampling is completed, the subject's hands will be washed with a bland soap (provided by the investigator) for approximately for thirty (30) seconds and rinsed for approximately fifteen (15) seconds. The subjects' hand will then be washed with Hibiclens® (4% chlorhexidine gluconate) for at least sixty (60) seconds. Subjects' hands and wrists will be rinsed with a 70% alcohol wash for ten (10) seconds. The subjects will rub the alcohol on all surfaces of their hands for fifteen (15) seconds and allow their hands to air dry.

A record of each disinfection procedure will be recorded on Source Document 1.

H. Plating and Incubation of the Organisms

Baseline specimens will be serially diluted in half-strength (0.0375 M) buffer (without Trtion X-100) in ten-fold dilutions to 10^{-3}, 10^{-4} and 10^{-5}. The diluted specimens will be plated using an automated plating system (Eddyjet system) onto MacConkey's agar. Post treatment specimens will be serially diluted in ten-fold dilutions to 10^{-1}, 10^{-2} 10^{-3} and 10^{-4}. Using an automated plating system (Eddyjet system), the undiluted and diluted specimens will be plated onto MacConkey's agar. The media for these analyses are shown in Appendix E.

Plated samples will be incubated aerobically for 18 - 24 hours at 35 $\pm$ 2°C. The plates will be analyzed using the Countermat®. The results will be reported as colonies per mL using the Countermat® software package.

The results will be recorded an electronic file created by the sponsor.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Data collection form (DCF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in DCF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or her designee.

A. Subject Inclusion Criteria

Subjects will be eligible for enrollment if they:

1. Are a male or female, over 18 years of age ;
2. Have signed a written informed consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/Dermatological/ Medical History Form (DCF 1);
4. Have hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders;
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

Subjects will not be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of arm or hand wash study within the past 7 days;
3. Have cuts, lesions, or other skin disorders on their hands or wrists;
4. Have soap, detergent, antibiotic, and/or perfume allergies;
5. Have eczema or psoriasis on their hands or arms;
6. Are using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos in the home within the last week (Appendix D);
7. Have excessively long or artificial nails (≥2 mm free edge) which would interfere with sampling;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator, would preclude participation.

D. Subject Number Assignment and Randomization

Upon entry into the study, each subject will be assigned a screening number beginning with 1001. Subjects will be assigned a permanent consecutive number, beginning with 001, as they are accepted into the study. This number will be used to identify the subject for the duration of the study.

IV. Study Material

A. Test Product

The test products will be sent by the Sponsor to the clinical site prior to study initiation. The test products will be identified with the appropriate label affixed to the outside of each container.

B. Shipping of Treatment Products and Other Study Supplies

The quantity of all treatment products and other study supplies, shipped to and returned from the clinical site, will be documented by the test site. The treatment products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc." with the facility's full address and phone number);
3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator(s) will insure that all test products and study materials, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11520 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Kathy Wiandt

V. Other Study Documentation

A. Adverse Events

Should any unexpected or serious adverse event occur during the clinical study or as a result of test product or study procedures, the subject will be requested to return to the site to be examined by the investigator or designee. The Investigator will determine if the adverse event is likely to be associated with product treatment or the study procedures. The investigator or other qualified medical personnel will determine if the event warrants termination of participation and/or to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward L. Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Kathy Wiandt, 513-626-5225 (work) or 513-398-6035 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in DCF 4. If treatment by a physician is necessary, this treatment will be documented on DCF 5.

The following criteria will be used to determine the reporting time frame.

1. Any serious adverse events or adverse events requiring immediate medical attention will be reported to the Sponsor's Monitor immediately (night or day) by telephone.
2. Adverse events resulting in subject termination from the study will be reported during the immediate business day by telephone.
3. Adverse events that do not require discontinuation of test participation can be reported during the immediate business day or next business day by telephone.

4. In the event of a serious adverse reaction, not necessarily related to use of the test product, or in the event of a death from any cause, the Investigator must report the event to the Sponsor's Monitor.

B. Protocol Amendments

If it becomes necessary to modify this protocol, the modification will be documented by a protocol amendment signed by the investigator and a representative of the Sponsor. All amendments to the final protocol will be consecutively numbered and will describe any changes made and the rationale for making the changes.

C. Protocol Deviations

If a deviation from the final protocol occurs, it is the responsibility of the Investigator, or designee, to notify the Clinical Research Associate or designee. The deviation and subsequent notification will be documented appropriately.

D. Study Monitoring

The Investigator will permit a representative of the Sponsor (usually the Clinical Research Associate) to visit the facility during the course of the study to monitor study progress. During the visit(s), the Investigator will permit the monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The study monitor will also be permitted to review and verify test articles, wash procedure, and any Investigator-generated or Sponsor-generated study documents. The monitor will document and discuss this visit with the Investigator, or his designee, including any problems that are to be resolved.

VI. Statistical Analyses

The sponsor will be responsible for all statistical analyses. For the bag juice results, each subject's base sampling CFU's will be compared to their test sampling CFU's using a nonparametric Wilcoxon paired signed-rank test. P-values ≤ 0.10 will be considered statistically significant. Percent change for each organism will be computed , if needed, by the following formula:

$$\left(1 - \frac{\text{geometric mean of the test CFU's}}{\text{geometric mean of the baseline CFU's}}\right) \times 100$$

VII. Investigator Responsibilities

A. Subject Informed Consent

All subjects will be informed as to the type of study, the general nature of the products being tested, and any known or anticipated adverse reactions that might result from participation. Each subject must provide the Investigator with written informed consent to serve as a participant in the study. Basic elements of informed consent are outlined in 21 CFR 50.25.

B. Final Report

The Sponsor will generate a final report of clinical results. The investigator will provide a detailed description of the adverse events and deviations from the protocol. The investigator will also include an accounting of the subjects screened, eliminated, enrolled and terminated. The Investigator will submit the legible copies of all data collection forms. The Sponsor may request one (1) copy of all case report forms before the Investigator's report is ready for submission to the Sponsor.

C. Record Retention

The Investigator will retain all study records in accordance with the test facility's SOP's.

D. Confidentiality

The Investigator and employees of the test facility are obligated to keep any information confidential regarding any of the personal cleansing products and all aspects of the study, as subject to the terms and conditions of the Laboratory Services Agreement between the test facility and Sponsor.

VIII. References

1. *Annual Book of ASTM Standards*, Volume 11.04, ASTM Designation: E 1174-94, Standard Test Method for "Evaluation of Health Care Personnel Handwash Formulation".

2. Tentative Final Monograph for Health-Care Antiseptic Drug Products; Proposed Rule, 21-CFR Parts 333 and 369, *Federal Register*, Volume 59, No. 116. June 17, 1994.

IX. Attachments

The following Appendices, Data collection forms are included as attachments to the Final Protocol:

A Written Informed Consent
B Subject's Follow-up Instructions
C Schedule of Test Period Procedures
D List of Representative Antibacterial/Antimicrobial Products
E Microbiological Media and Methods

Data Collection Forms

1 Demographics/Dermatological/Medical History Form
2 Inclusion/Exclusion Form
3 Follow- up Visit
4 Adverse Event
5 Physician's Report Form

Source Documents

1 Treatment Phase (Baseline, Wash 1 and Wash 10)
2 Treatment Phase (Washes 2 through 9)
3 Shipping of Microbiological Specimens

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Kathy Wiandt, B.A., Clinical Research Associate
Clinical Research and Biometrics Department

Date: 4/18/01

STATISTICIAN:

Jeanne C. Philippo, B.A., Statistician
Clinical Research and Biometrics Department

Date: 4/18/01

APPROVED BY:

Ward L. Billhimer, M.S., Senior Scientist
Clinical Research and Biometrics Department

Date: 4/19/01

Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator(s) for CRB-01-04-063-HB:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies.

Gayle K. Mulberry, M.S., Investigator — Date: 4/19/01

Kathleen A. Baxter, B.S., Sub-Investigator — Date: 4.19.01

Ann R. Brady, A.S., Sub-Investigator — Date: 4.18.01

Appendix A
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WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B
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SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Efficacy Evaluation Of Three Handwipe Products Modified Health Care Personnel Handwash Study Versus *Escherichia Coli*". During this study, a quantity of bacteria (*E. coli)* was placed on the surface of both your hands. Although we do not expect you to have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your hands and wrists within four (4) to nine (9) days.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your hands and wrists daily. If you notice the appearance of any pimples, blisters or raised bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:00 am-5 p.m.) or at (513) 831-3354 after hours.

You are required to return to the test site for a follow-up visit. Your follow-up is scheduled for:

_____

Date Time

Thank you for your cooperation.

Appendix C
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SCHEDULE OF TEST PERIOD PROCEDURES

1. **Practice treatment Nice 'n' Clean®:**
   - towelette is placed in subjects' left hand
   - subject will rub all surfaces of their right hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips
   - subject transfers towelette to right hand
   - subject will rub all surfaces of their left hands and wrist for 15 seconds including palmar surface, back of hand, fingers and web area between fingers, and finger tips

2. **70% alcohol rinse**
   - squirt backs and palms of subjects' hands with 70% alcohol for 10 seconds
   - subjects rub alcohol over hands for 15 seconds
   - subjects rinse hands under running tap water for 15 seconds
   - subjects dry hands with paper towels

3. **Base contamination**
   - dispense 1.5 mL aliquot of bacterial suspension onto both subjects' hands
   - subjects rub aliquot over hands for 20 seconds
   - allow subjects' hands to air dry for approximately 30 seconds
   - repeat application 2 times
   - allow subjects' hands to air dry 1 minute after the last application

4. **Base sampling**
   - place bags on subject's right and left hands
   - dispense 75 mL stripping solution into each bag
   - secure bags
   - massage for 1 minute
   - sample each bag

5. **Water rinse**
   - subjects rinse hands with water for 30 seconds

6. **70% alcohol rinse**
   - perform as above

7. **Test contamination (prior to Test Product treatments 1 through 10)**
   - perform as above under base contamination

8. **Test Products Treatments (treatments 1 through 10)**
   - perform as described under practice treatment
   - for treatments #1 and #10, hands will not be dried prior to sampling
   - for treatments # 2 through #9 subjects will dry hands with paper towels

9. **Test sampling - Following Treatment 1**
   - perform as above under base sampling

- subjects rinse hands with water for 30 seconds after the first test sampling

Appendix C (*continued)*
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10. Test sampling - Following Treatment 10

- place bag on of the subject's hands
- dispense 75 mL stripping solution into the bag
- secure bag
- massage for 1 minute
- sample bag

11. Disinfection

- subject rinse hands for thirty (30) seconds
- squirt subjects' hands with 2 mL of bland soap
- subjects wash hands and wrists for approximately 30 seconds
- subjects rinse hands and wrists for approximately 15 seconds
- squirt subjects' hands with 5 mL of Hibiclens®
- subjects wash hands and wrists for at least 60 seconds
- subjects rinse hands and wrists for 15 seconds
- squirt backs, palms and wrists of subjects' hands with 70% alcohol for 10 seconds
- subjects rub alcohol over hands and wrists for 15 seconds
- subjects' hands will be allowed to air dry

Appendix D
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LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Antibacterial Dishwashing Liquids

Dawn
Joy
Dial
Palmolive

Appendix E
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MICROBIOLOGICAL MEDIA AND METHODS

0.075M Phosphate Buffer Solution with Neutralizers

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO_4, 5.0 grams of Polysorbate (Tween) 80, 0.7 grams of lecithin, and 1.0 gram of Triton X-100. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ± 0.1 with 1 N HCl or 1 N NaOH. Dispense buffer in bottles so that after autoclaving the volume equals 75 ± 1 mL. Loosely cap bottles and sterilize in the autoclave at 121°C.

0.0375M Phosphate Buffer Solution with Neutralizers

Weigh 0.2 grams of KH_2PO_4, 5.05 grams of Na_2HPO_4, 5.0 grams of Polysorbate (Tween) 80 and 0.7 grams of lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 ±0.1with 1 N HCl or 1 N NaOH. Dispense buffer in appropriate volumes. Loosely cap vessels and sterilize in the autoclave at
121°C.

MacConkey's Agar

Suspend 50 grams in 1 liter of distilled or deionized water. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45-50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Data Collection Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108589-11 CRB-01-04-063-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male(1) ☐ Female(2)	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER	No	Yes	Don't Know
1. Psoriasis ?			
2. Eczema ?			
3. Skin Cancer ?			
4. Skin Allergies ? Please specify:			
5. Hives ?			

Does the Subject have any of the following (present and past) ?

II. OTHER MEDICAL INFORMATION	No	Yes	Don't Know
1. Allergies.? Please specify.			
2. Hepatitis ?			
3. Heart and Vascular Disease?			
4. Liver Disease ?			
5. Kidney Disease ?			
6. Tuberculosis ?			
7. Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8. Cancer ?			
9. Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10. Organ transplant ?			
11. Any other condition not listed ? Please specify:			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION	No	Yes	Don't Know
1. Antibiotics, oral or systemic ?			
2. Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3. Heart Medication ?			
4. Insulin ?			
5. Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: _____/_____/_____ mm dd yy

Data Collection Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108589-11 CRB-01-04-063-HB		Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA

Check one YES	NO	Subject:
		1. Is ≥ 18 years ?
		2. Has signed informed consent?
		3. Is healthy as evidenced by responses on DCF 1 ?
		4. Has hands and wrists that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA

YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility?
			2. Has participated in any type of hand or arm wash study within the past 7 days?
			3. Has cuts, lesions, or other skin disorders on their hands or wrists?
			4. Has soap, detergent, antibiotic and/or perfume allergies?
			5. Has eczema or psoriasis on their hands or wrists?
			6. Has used antibacterial/antimicrobial soaps, medicated lotions and creams and/or anti-dandruff shampoos within the last week?
			7. Has long (≥ 2 mm free edge) or artificial nails
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Data Collection 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Interviewer's Signature	Date: ___/___/___ mm dd yy
Investigator's Signature::	Date: ___/___/___ mm dd yy

TREATMENT PHASE

Study #	Hill Top Research, Inc.	Permanent #'s
01-108589-11 CRB-01-04-063-HB		

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Test Contamination Procedure #2	am/pm	☐ Yes / ☐ No	
Test Product Treatment #2	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #3	am/pm	☐ Yes / ☐ No	
Test Product Treatment #3	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #4	am/pm	☐ Yes / ☐ No	
Test Product Treatment #4	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #5	am/pm	☐ Yes / ☐ No	
Test Product Treatment #5	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #6	am/pm	☐ Yes / ☐ No	
Test Product Treatment #6	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #7	am/pm	☐ Yes / ☐ No	
Test Product Treatment #7	am/pm	☐ Yes / ☐ No	Water Temp: °F
Test Contamination Procedure #8	am/pm	☐ Yes / ☐ No	
Recorder's Signature:		Date: ____/____/____	
Reviewer's Signature:		Date: ____/____/____	

Source Document 2 (*continued*)

TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108589-11 CRB-01-04-063-HB			

Test Product Treatment #8	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Contamination Procedure #9	am/pm	☐ Yes / ☐ No	
Test Product Treatment #9	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Recorder's Signature:		Date: _____/_____/_____	
Reviewer's Signature:		Date: _____/_____/_____	

Source Document 1

TREATMENT PHASE

Study #	Hill Top Research, Inc.		Permanent #'s
01-108589-11 CRB-01-04-063-HB			

EVENT	TIME	PROCEDURE PERFORMED ACCORDING TO PROTOCOL?	
Practice Wipe	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	
Base Contamination Procedure	am/pm	☐ Yes / ☐ No	
Base Bacterial Sampling Procedure	am/pm	☐ Yes / ☐ No	
Base Decontamination	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #1	am/pm	☐ Yes / ☐ No	
Test Product Treatment #1	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #1 (after first treatment)	am/pm	☐ Yes / ☐ No	
Test Contamination Procedure #10	am/pm	☐ Yes / ☐ No	
Test Product Treatment #10	am/pm	☐ Yes / ☐ No	**Water Temp:** °F
Test Bacterial Sampling Procedure #2 (after 10th treatment)	am/pm	☐ Yes / ☐ No	
Decontamination	am/pm	☐ Yes / ☐ No	**Water Temp:** °F

Recorder's Signature:	Date: _____/_____/_____
Reviewer's Signature:	Date: _____/_____/_____

Data Collection Form 3

FOLLOW-UP VISIT

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
01-108589-11 CRB-01-04-063-HB		Follow-up	____/____/____ mm dd yy	____/____/____ F M L	Permanent #:

Date Subject Entered the Study:	Follow-up Visit Date :
____/____/____ mm dd yy	____/____/____ mm dd yy

Does the subject's hands have the presence of pimples, blisters, or raised itching bumps surrounded by erythema and/or edema that may be indicative of a skin infection ?

YES NO If yes, complete below:

Clinical Observations: (Include date of onset and descriptions severity locations, etc.)

_____

_____

Comments: _____

_____

_____

_____

_____

_____

Has the subject had any health related issues since the treatment procedure?

YES NO If yes, complete below:

Comments: _____

_____

_____

_____

_____

_____

Investigator's Signature or designee	Date
	____/____/____ mm dd yy

Data Collection Form 4

ADVERSE EVENT

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108589-11 CRB-01-04-063-HB			___ ___/___ mm dd yy	___/___/___ F M L	Permanent #:

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician

☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm dd yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
			/ /	
			/ /	
			/ /	

Investigator's Signature:	Recorded by:	Date ___/___/___ mm dd yy

Data Collection Form 5

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.		Date	Subject Initials	Subject Screen #
01-108589-11 CRB-01-04-063-HB			___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature _____ Date

Source Document 3
HT# 01-108589-11
CRB-01-04-063-HB

TRANSFER OF MICROBIAL SPECIMENS

SPECIMENS TAKEN TO THE LABORATORY	SPECIMENS RECEIVED
Date: _____ Time: _____	Date Received: _____
Test Site: _____	Time: _____
Method of Transport: _____	Laboratory: _____
Samples Packed as specified: Yes _____ No _____	Cold storage intact? Yes _____ No _____

LISTING OF SPECIMENS			SPECIMENS RECEIVED	
Subject No.	**Sample No.**	**Time Collected**	**✓= OK D = Lost / Damaged NR = Not Received**	**Time Plated**

Shipping Technician: _____ Date: _____	Receiving Technician: _____ Date: _____

Study Title: "Efficacy Evaluation of Three Handwipe Products In a Modified Health Care Personnel Handwash Study Versus *Escherichia coli*"

CONSENT FORM

INTRODUCTION: You are being asked to take part in a research study. Before you give your consent to be a subject, it is important that you take enough time to read and understand what your participation would involve. In preparing this consent form, it has been necessary to use some technical language. Please ask questions if there is anything you do not understand.

You will be given a signed copy of this consent form and any other necessary written information prior to the start of the study.

PURPOSE: The purpose of this research study is to determine the effectiveness of three handwipe products containing an antibacterial ingredient against bacteria found on the skin. Approximately twenty (20) people at least 18 years of age will be screened as potential subjects in this study. At least twelve (12) subjects are expected to complete the two-visit study.

TEST ARTICLES: You will be assigned 1 of the three antibacterial handwipe products. The handwipe products are experimental.

STUDY PROCEDURES: Prior to enrollment in the test, you will be asked to complete a brief medical history questionnaire and another form to determine your eligibility for the study. Your hands and wrists will be checked for visible cuts, scratches or rashes on them. It is possible that you may not be able to participate based on your answers to these questions or the condition of the skin on your hands and wrists.

If you are selected to participate in this study, you will be instructed to perform a practice treatment with a handwipe product. Then, your hands will be rinsed with alcohol, rubbed for about 15 seconds and rinsed in tap water for 15 seconds followed by drying with paper towels. Afterwards, your hands will be contaminated with a watery liquid containing relatively non-harmful bacteria (*Escherichia coli*). This liquid containing the bacteria will be spread over the surfaces of the hands, and the hands will be allowed to air dry. Following air drying, the hands will be sampled. Sampling is accomplished by having you place your hands into large plastic bags to which will be added a mild soap-like solution. A laboratory technician will massage each bagged hand for one minute. The hands will be removed from the bags and the solution from each bag will be tested to determine the number of test bacteria added to the hands. Following this baseline sampling, the hands will be rinsed for 30 seconds with tap water, rinsed with 70% alcohol and water, then dried with paper towels. Then the hands will be contaminated as above and treated with the assigned test material, 1

of the 3 handwipe products following specific directions. After the treatment with the handwipe product, your hands will be sampled as above about 4-5 minutes after the first treatment is completed to determine the number of bacteria removed or killed by treatment. Your hands will be contaminated and treated 10 times. After the 10th treatment, sampling will be repeated. Following each sampling, your hands will be rinsed with tap water. After the final sampling your hands will then be washed with a plain soap followed by a wash with Hibiclens®, an antimicrobial soap, and rinsed with alcohol prior to leaving the lab.

After completing the treatment visit and until your follow-up visit, you will need to check the skin on your hands each day for any pimples, bumps or rashes. Within four to nine days after you have completed treatment, you will be required to return to the lab for a follow-up visit. Your hands will be checked for infection by a technician trained in observing infection.

FEMALES OF CHILDBEARING POTENTIAL: You may not participate in this study if you are pregnant or nursing. As part of giving your consent you must agree to have a urine pregnancy test at the start of the study.

RISKS: The risks associated with this test are primarily related to infection with the test bacteria. For healthy persons, the possibility of a skin infection exists; however, this possibility is remote because, (1) test bacteria are applied only to healthy or uninjured skin, and (2) the skin is cleansed with antibacterial products following contact with the test bacteria. Your hands may also show a "reaction." A "reaction" could be pimples, blisters or raised bumps surrounded by redness and/or swelling. It is unlikely, but possible, that a rash could develop.

No risks to you as a study participant, other than those described above as "reactions," are anticipated during the study. Reactions are usually due to irritation, although an allergic reaction might occur. If you become allergic, it is possible that future exposures to the same ingredient may cause a skin reaction. If this occurs, you will be provided with information to minimize the chance for future exposures.

You may experience risks or side effects that are not known at this time. You will be informed in a timely manner if new information becomes available that may influence your willingness to continue in this study.

BENEFITS: You will not benefit from the application of test product but the study results may allow a new or improved product to be marketed.

ALTERNATIVE PROCEDURES/TREATMENTS: Because you are not being treated for a medical condition, alternative treatments do not apply to this study.

CONFIDENTIALITY: Information concerning you that is obtained in connection with this study will be kept confidential by Hill Top Research, except that the sponsoring company whose product is being tested will receive a copy of the study records. The records will be coded to protect your identity. In addition, government regulatory agencies, including the U.S. Food and Drug Administration (FDA), may inspect the records of the study. Information obtained in the study may be used for medical or scientific publication, but your identity will remain confidential.

MEDICAL TREATMENT: If in the course of this study you experience illness, discomfort or injury that appears to be a result of the study, Hill Top Research will provide you with medical care at no cost to you. Providing such medical care is not an admission of legal responsibility. If such illness, discomfort or injury does occur, ask any staff member to arrange a meeting for you with the appropriate personnel.

In certain cases of illness or injury resulting from this study, workers' compensation coverage may be available. In accordance with Ohio law, Hill Top Research has secured workers' compensation coverage for participants in its studies and tests, and has paid and will pay appropriate premiums into the State Insurance Fund on behalf of such participants.

WHO TO CONTACT: If you have any questions about this study or in case of an emergency, contact Stacey, Study Coordinator at 513-831-3114, ext. 2324 during business hours (M-F, 8:00 A.M. - 5:00 P.M.) or Ann Brady, Study Manager at 513-831-3354 after hours.

VOLUNTARY PARTICIPATION/WITHDRAWAL: Your participation in this research study is strictly voluntary. You may refuse to participate or may discontinue participation at any time during the study without penalty or loss of benefits to which you are otherwise entitled.

If you agree to participate in this study, you are also agreeing to provide Hill Top Research with accurate information and to follow study instructions as given to you. If you fail to comply with study procedures, your participation may be terminated.

Your participation in the study may be discontinued at any time without your consent by the Investigator, the FDA, or the sponsoring company.

COMPENSATION: You will be paid $55.00 for the completion of this study. You will be compensated according to the following schedule:

If you do not qualify	Visit 1	you will receive	$10.00
If you qualify but are eliminated as an extra subject	Visit 1	you will receive	$15.00
If you complete	Visit 1	you will receive	$30.00
If you complete	Visit 2	you will receive	$55.00

Payments will be made at the end of the study.

There are no anticipated expenses to you for participating in this study. All test related materials will be provided at no cost to you.

CONSENT TO PARTICIPATE

I know that my participation in this study is voluntary and that I have the right to refuse to participate. I know that I may withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled. If I withdraw or am dismissed for failure to obey rules or follow directions, I understand I will only be paid for the portion of the study that I have completed. If, in the judgment of the Investigator, it is best to discontinue my participation in the study for other reasons, I will be paid either in full or for that portion of the study already completed.

If I am a female of childbearing potential, I am not currently pregnant or nursing an infant. I am using an adequate means of birth control and, if I become pregnant or believe I have become pregnant, I will notify the Investigator immediately.

CONSENT: I have read all of the above information and have been given an opportunity to ask questions about this study. Answers to such questions (if any) were satisfactory. I am eighteen years of age or older and freely and without reservation give my consent to serve as a subject in this study. By signing this form, I have not given up any of my legal rights as a research subject.

_____

Subject's Name Printed: First Middle Initial Last

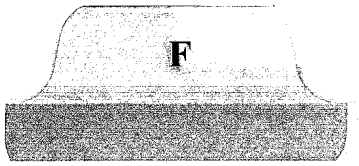
_____

Subject's Signature Date

_____

Signature of Person Conducting Consent Discussion Date

SUBJECT SCREEN NO. _____
SUBJECT NO. _____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FINAL REPORT OF CLINICAL TEST RESULTS

From: P. B. Neumann, J. S. Englehart

Date: July 10, 1998

To: Study File for CRB-97-11-245-CD

Retention Limit: Until Superseded
Released: WLB 7/10/98

Subject: Residual Effectiveness Screening Test Results on B-22M Liquid Soap Formulations with Varying Levels of Salicylic Acid and Triclosan (TCS) and Liquid Ivory® against *E. coli* - Hill Top Research, Inc., CRB-97-11-245-CD, HT 97-5425-11

Summary:

The results of this clinical study show that B-22M liquid soap formulations with either no TCS, 0.5% TCS or 1.0% TCS and no salicylic acid (codes A, B and C, respectfully) were not significantly more effective than Liquid Ivory, code J, at lowering the levels of *Escherichia coli* inoculated on the skin (p-value <0.10). All other B-22M liquid soap formulations with either 0.5% or 1.0% salicylic acid and varying levels of TCS, ranging from none to 1.0%, were significantly more effective than Liquid Ivory at lowering organisms inoculated on the skin.

The results are summarized in the attached tables.

Objective:

The objective of this study was to evaluate the residual effectiveness of ten (10) liquid soap products against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection.

Test Products:

Code	Test Product	Active Ingredient	TSIN
A	B-22M	none	BI0060-108
B	B-22M	0.5% TCS	BI0060-110
C	B-22M	1.0% TCS	BI0060-112
D	B-22M, 0.5% salicylic acid	none	BI0060-100
E	B-22M, 0.5% salicylic acid	0.5% TCS	BI0060-102
F	B-22M, 0.5% salicylic acid	1.0% TCS	BI0060-104
G	B-22M, 1.0% salicylic acid	none	BI0060-092
H	B-22M, 1.0% salicylic acid	0.5% TCS	BI0060-094
I	B-22M, 1.0% salicylic acid	1.0% TCS	BI0060-096
J	Liquid Ivory Soap	none	BI0060-126

Study Design:

This study was conducted at Hill Top Research, Inc. in Miamiville, Ohio on December 1, 1997. This was a randomized, split forearm wash study to evaluate the residual antibacterial effectiveness of ten (10) liquid products. Thirty (30) male and female subjects, ages 18 through 65 years old, who did not regularly use

Study Design: ***(continued)***

antibacterial soap, medicated lotion or cream, and/or antidandruff shampoo were enrolled. For the test procedure, each of the subject's forearms was divided into an upper and lower treatment area, for a total of four (4) treatment areas per subject. Each treatment area was washed one (1) time for forty-five (45) seconds. Within five (5) minutes after the wash with the test products was completed, a 3.0 cm circular test site was marked-off in each area. Each circular site was then inoculated with 10 µL of a 24 hour broth culture of *E. coli* grown in Trypticase Soy Broth (TSB) and occluded with a 24 mm Hill Top Chamber® that was taped to the skin with Durapore® tape. One (1) hour after inoculation, the surviving organisms were harvested from each occluded site using the Williamson-Kligman scrub technique. The specimens from each site were plated on Trypticase Soy Agar with polysorbate (Tween) 80 and incubated for 18 - 24 hours at 35 ±2°C. The colony forming units (CFU's) of *E. coli* were counted at the end of the incubation period to determine the number of surviving organisms at each of the treated sites.

Data Analysis:

The surviving colony forming units (CFU's) of bacteria for each subject were enumerated. The numbers of bacteria were converted to base 10 logarithms. The $\log_{10}$ CFU counts were compared using analysis of variance techniques. Factors were treatment levels and subject, adjusting for subject to subject variability, side (right vs. left) variability, site (upper vs. lower) variability, and site to side variability, to estimate which of the test products had the greatest activity. P-values ≤ 0.10 were considered statistically significant.

Subject Accountability:

Thirty (30) subjects were enrolled and completed this study.

Adverse Events:

None reported.

Submitted by:

Paula B. Neumann

Jan S. Englehart

Conclusions:

The three B22M prototypes with no salicylic acid were not significantly more effective than Liquid Ivory Soap. All other prototypes were significantly more effective against *E. coli* at p-values ≤ 0.10.

Salicylic acid was a significant factor (p-value = 0.0044) in efficacy against E. coli, whereas TCS was not (p-value = 0.4652).

Both the 0.5% and 1% salicylic acid B22M prototypes were significantly more effective than Liquid Ivory Soap even when TCS was not present at p-values ≤ 0.10.

Although the interaction between TCS and salicylic acid was not significant, (p-value = 0.1386) it was close enough to significance to merit examination. It appears as though some salicylic acid was necessary to provide a dose response with TCS in the ranges examined in this study and that this response is greater than 0.5% salyclic acid. See Figures 1 & 2.

Treatment	Code	N	Mean	Std. Dev.
B22M, 0.0% TCS, 0.0% Salicylic Acid	A	12	4.9	0.546
B22M, 0.5% TCS, 0.0% Salicylic Acid	B	12	5.2	0.524
B22M, 1.0% TCS, 0.0% Salicylic Acid	C	12	5.0	0.510
B22M, 0.0% TCS, 0.5% Salicylic Acid	D	12	4.3	1.086
B22M, 0.5% TCS, 0.5% Salicylic Acid	E	12	4.1	1.292
B22M, 1.0% TCS, 0.5% Salicylic Acid	F	12	4.0	0.967
B22M, 0.0% TCS, 1.0% Salicylic Acid	G	12	4.2	0.713
B22M, 0.5% TCS, 1.0% Salicylic Acid	H	12	3.8	0.936
B22M, 1.0% TCS, 1.0% Salicylic Acid	I	12	3.5	1.411
Liquid Ivory Soap	J	12	5.3	0.6074

One Way Layout Ignoring DOX Design:

Treatment	LSMean	Std. Error
A	4.7	0.220
B	4.9	0.220
C	5.0	0.220
D	4.4	0.220
E	4.4	0.220
F	4.3	0.220
G	4.3	0.220
H	3.9	0.220
I	3.4	0.220
J	5.1	0.220

Overall P-value=0.0001

Pairwise P-values (One Way Layout Ignoring DOX Design)

i/j	A	B	C	D	E	F	G	H	I	J
A	.	0.4224	0.2858	0.3409	0.3661	0.3463	0.3438	0.0234	0.0001	0.1145
B	0.4224	.	0.7357	0.0793	0.0997	0.1066	0.1109	0.0052	0.0001	0.4608
C	0.2858	0.7357	.	0.0284	0.0396	0.0474	0.0595	0.0025	0.0001	0.6923
D	0.3409	0.0793	0.0284	.	0.9976	0.9598	0.9659	0.2017	0.0071	0.0273
E	0.3661	0.0997	0.0396	0.9976	.	0.9548	0.9614	0.1790	0.0065	0.0290
F	0.3463	0.1066	0.0474	0.9598	0.9548	.	0.9959	0.1681	0.0050	0.0245
G	0.3438	0.1109	0.0595	0.9659	0.9614	0.9959	.	0.1409	0.0029	0.0184
H	0.0234	0.0052	0.0025	0.2017	0.1790	0.1681	0.1409	.	0.0766	0.0002
I	0.0001	0.0001	0.0001	0.0071	0.0065	0.0050	0.0029	0.0766	.	0.0001
J	0.1145	0.4608	0.6923	0.0273	0.0290	0.0245	0.0184	0.0002	0.0001	.

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Salicylic Acid	LSmean	Std. Error
1 = 0.0%	4.8	0.162
2 = 0.5%	4.3	0.152
3 = 1.0%	3.9	0.162

Overall P-value = 0.0044

Pairwise P-values

	1	2	3
1	.	0.0428	0.0011
2	0.0428	.	0.0618
3	0.0011	0.0618	.

TCS	LSMean	Std. Error
1 = 0.0%	4.5	0.120
2 = 0.5%	4.4	0.120
3 = 1.0%	4.2	0.120

Overall P-value = 0.4652

Pairwise P-values

	1	2	3
1	.	0.7083	0.2287
2	0.7083	.	0.4029
3	0.2287	0.4029	.

Salicylic Acid	TCS	LSMean	Std. Error
1 = 0.0%	0.0%	4.6	0.239
2 = 0.0%	0.5%	4.9	0.244
3 = 0.0%	1.0%	5.0	0.242
4 = 0.5%	0.0%	4.4	0.235
5 = 0.5%	0.5%	4.3	0.234
6 = 0.5%	1.0%	4.3	0.235
7 = 1.0%	0.0%	4.4	0.242
8 = 1.0%	0.5%	3.9	0.244
9 = 1.0%	1.0%	3.4	0.239

Overall P-value = 0.1386

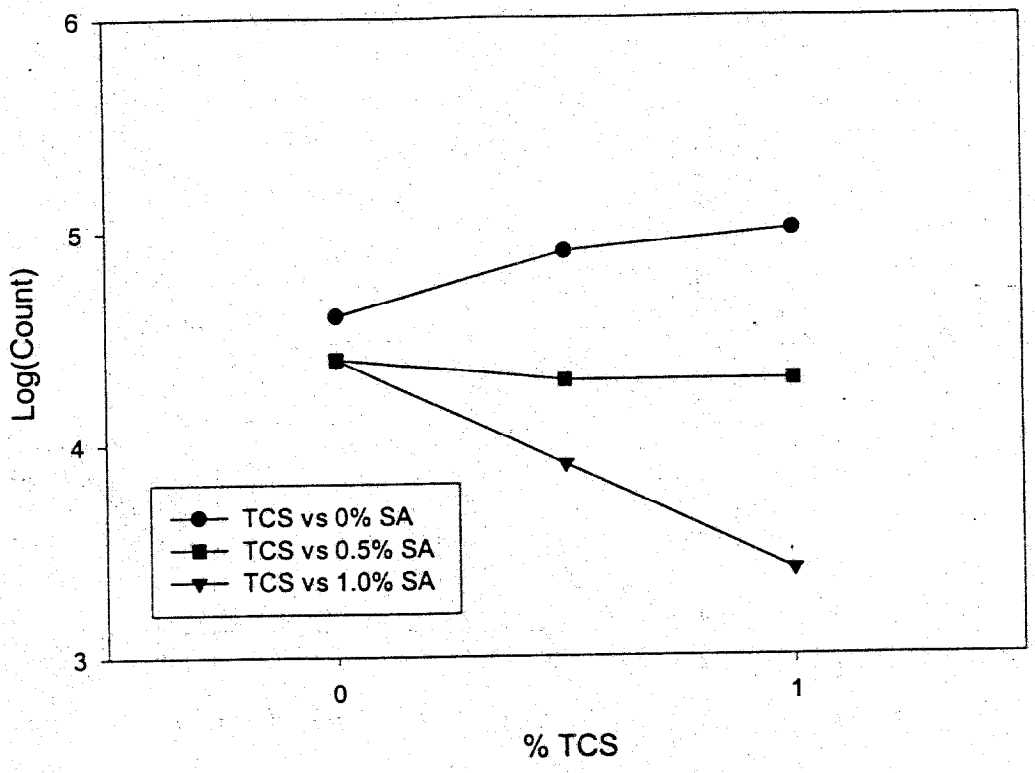
Pairwise P-values:

i/j	1	2	3	4	5	6	7	8	9
1	.	0.4355	0.3262	0.3871	0.4214	0.4118	0.4429	0.0484	0.0005
2	0.4355	.	0.7861	0.1022	0.1317	0.1468	0.1739	0.0148	0.0001
3	0.3262	0.7861	.	0.0450	0.0638	0.0791	0.1107	0.0084	0.0001
4	0.3871	0.1022	0.0450	.	0.9861	0.9846	0.9809	0.2544	0.0150
5	0.4214	0.1317	0.0638	0.9861	.	0.9695	0.9923	0.2207	0.0128
6	0.4118	0.1468	0.0791	0.9846	0.9695	.	0.9614	0.2003	0.0095
7	0.4429	0.1739	0.1107	0.9809	0.9923	0.9614	.	0.1559	0.0053
8	0.0484	0.0148	0.0084	0.2544	0.2207	0.2003	0.1559	.	0.1046
9	0.0005	0.0001	0.0001	0.0150	0.0128	0.0095	0.0053	0.1046	.

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

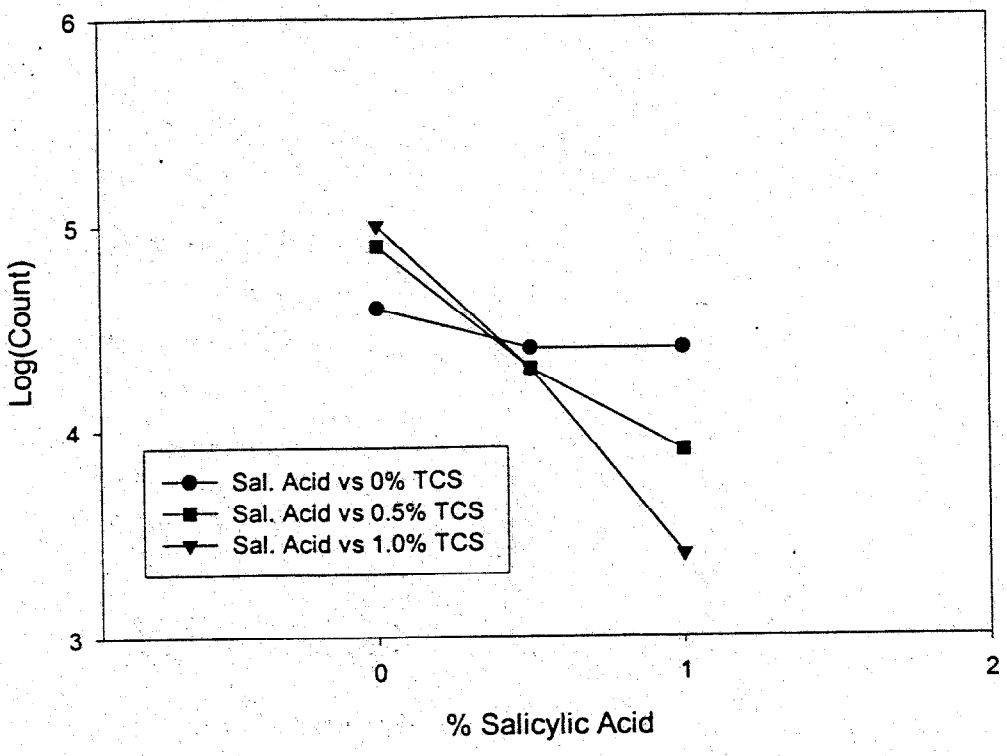
P. B. Neumann

Figure 1 - Plot of Log(Count) by %TCS and % Salicylic Acid



P. B. Neumann

Figure 2 - Plot of Log(Count) by % TCS and % Salicylic Acid



P. B. Neumann

RESIDUAL EFFECTIVENESS SCREENING TEST OF ANTIBACTERIAL LIQUID PRODUCTS AGAINST *E. COLI*

Study Number:	CRB-97-11-245-CD
Study Identification:	HT# 97-5425-11
Principal Investigator:	Gayle K. Mulberry, M.S.
Sub-Investigator	Ann R. Brady, A.S.
Clinical Test Site:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Sponsor:	The Procter & Gamble Company Clinical Research and Biometrics Division Personal Cleansing Sector 11511 Reed Hartman Highway Cincinnati, Ohio 45241
Sponsor Representative:	Ward L. Billhimer, M.S.
Sponsor Statistician:	Paula B. Neumann, Ph.D.
Sponsor Toxicologists:	Paul F. Sterchele, Ph.D. J. David Innis, Ph.D.
Clinical Research Associates:	Jan S. Englehart, B.S., ASCP
Start Date:	December 1, 1997

Confidentiality: The obligations of the Investigator, regarding the confidential information on the antibacterial soap and all aspects of the study will be kept confidential according to the agreement with The Procter & Gamble Company.

I. Study Objective

The objective of this study is to evaluate the residual effectiveness of ten (10) liquid soap products containing an antibacterial active against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection.

II. Study Summary

This is a randomized blinded clinical study that will evaluate the residual effectiveness of ten (10) liquid soap products using a split forearm test design. It will consist of a one (1) day test period. Thirty (30) male and female subjects, age 18 to 65 years, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and/or anti-dandruff shampoos will be enrolled into the study. During this study, thirty (30) subjects will be used to evaluate ten (10) test products.

On the day of the test, subjects will report to the clinical test facility. Each of the subjects' forearms will be divided into an upper and lower treatment area for a total of four (4) treatment areas. Subjects will have each of their forearms washed by a laboratory technician with the test products according to a randomization.

Following treatment with the test products, a test site will be marked off in the center of each treatment area on the forearms. Each of the four (4) test sites will be inoculated with a known amount of *Escherichia coli* (ATCC 11229) grown in Trypticase Soy Broth (TSB). The test sites will then be occluded with a Hill Top Chamber® patch for one (1) hour. After occlusion, the patches will be removed and the bacteria on the skin will be harvested using a scrub technique [1]. Each sample of harvested bacteria will be diluted, plated, and incubated. Following incubation, the number of surviving colony forming units (CFU's) for each site will be determined.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Case Report Form (CRF)1]. Only subjects meeting the inclusion/exclusion criteria, outlined in CRF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or his designee.

A. Subject Inclusion Criteria

Subjects are eligible for enrollment if they:

1. Are a male or female, age 18 to 65 years;
2. Have signed the Informed Consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/ Dermatological/Medical History Form (CRF 1);
4. Have forearms that are free of dermatoses, cuts, lesions, and other skin disorders; and
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

A subject cannot be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of hand or arm wash study within the past 14 days;
3. Have cuts, scratches, or a rash on the volar surface of either forearm;
4. Have soap, detergent, and/or perfume allergies;
5. Have eczema or psoriasis on their arm(s);
6. Have taken systemic antibiotics or used topical antibiotics for any reason in the three (3) weeks prior to the start of the study;
7. Are currently using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been medically diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator would preclude participation.

IV. Study Design and Procedures

A. Randomization

The Sponsor will generate the study randomization for the assignment of treatment products. Each subject will be assigned to a treatment number which will become their permanent subject identification number. All subjects and site personnel, including the Investigator, will remain blinded to product identities.

B. Study Schedule

On the day of the test, prospective subjects will visit the test facility to complete a written informed consent, (Appendix A), the Demographics/Dermatological/ Medical History Form (CRF 1), and the Inclusion/Exclusion Form (CRF 2). Subjects who meet the study criteria, will be randomly assigned to a treatment regimen. Two (2) treatment areas, upper and lower, will be marked off on each arm. A lab technician will wash each of the treatment areas with one (1) of the test products according to the procedure described in Appendix C. After the wash with the test products is completed, a test site will be marked-off in the center of each treatment area on the subjects' forearms. These sites will be inoculated, occluded, and harvested according to the procedures described below.

To ensure that any delayed adverse events, primarily skin infections, are reported to the study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study Completion (Appendix B) before leaving the clinical test facility after they have completed the study. This sheet will instruct the subjects to examine their forearms 48 - 72 hours after completion of the study for the presence of pimples, blisters, or raised red itching bumps surrounded by erythema and/or

edema that may be indicative of a skin infection. Subjects, who notice any of these lesions, will be instructed to call the clinical test site.

C. Wash with the Test Products

Two (2) 10 x 5 cm treatment areas (upper and lower) will be marked off on each subject's forearms using a template. Each of the four (4) treatment areas on the subjects' forearms will be washed by a laboratory technician according to the procedure outlined in Wash Procedure, Appendix C. Each treatment area will be washed one (1) time with the appropriate test product. A record of the subject washes will be kept on CRF 3. In general, the following should be noted: water temperature should be closely monitored and maintained at 95-100°F. The water temperature should be recorded. Wash time should be recorded at the start of washing.

D. Microbial Inoculation

Within five (5) minutes after the wash with the test products is completed, one (1) circular test site will be marked-off in each treatment area of the subject's forearms. These circular sites will be spaced in the center of each treatment area of the forearm. They will be made by pressing a 3.0 cm diameter glass cylinder, inked with a stamp pad, against the skin.

All test sites on both arms will be inoculated with *E. coli* (ATCC 11229) that has been grown in Trypticase Soy Broth (TSB). To determine the actual number of CFU/mL at the time of inoculation, the broth culture to be used for inoculation will be plated.

Using an Eppendorf® pipette, the skin area delineated by the cylinder will be inoculated with 10 µL of the bacterial culture to obtain 10^6 to 10^7 colony forming units (CFU's) of *E. coli*. A sterile, disposable, inoculating loop will be used to evenly spread the inoculum within the center of the test site while remaining 4 to 5 mm from the marked edge. Inoculation of each site will be documented on CRF 3.

E. Occlusion of the Test Sites

The inoculated test site will be immediately occluded by covering it with a small plastic bowl (25 mm Hill Top Chamber® with pad removed) that will be secured to the skin with an adhesive dressing (Durapore®, 3M). The time of occlusion will be recorded on CRF 3.

F. Harvesting of the Surviving *E. coli* Organisms

All inoculated sites will be harvested for surviving organisms at 1 hour $\pm$ 5 minutes after inoculation. The time of harvesting will be recorded on CRF 3.

The following procedure will be used for harvesting:

1. A hollow glass cylinder 2.2 cm in diameter will be positioned in the middle area of the test site avoiding contact with the ink-stamped edge.
2. 1.0 mL of phosphate-buffered 0.1% Triton X-100 detergent (pH 7.9), with suitable neutralizers, will be pipetted into the cylinder.
3. The skin inside the cylinder will be massaged for 60 seconds with a Teflon policeman.
4. The fluid will be removed by pipetting it into an empty sterile culture tube.
5. Another 1.0 mL of buffered detergent will be added for a second 30 second scrub.

6. The fluid from the second scrub will be removed and pooled with the fluid from the first scrub.

G. Disinfection of the Test Sites

After each test site is harvested, it will be disinfected with 70% isopropyl alcohol. When the harvesting of the last test site is completed, both forearms will be washed for approximately thirty (30) seconds with Hibiclens® (4% chlorhexidine gluconate). After the arms have been washed with Hibiclens®, a small amount of Polysporin® antibiotic ointment will be applied to each test site.

H. Plating and Incubation of the Organisms

Specimens from each of the four (4) sites will be plated within four (4) hours after harvesting. For plating, they will be serially diluted in half-strength (0.0375 M) buffer in ten-fold dilutions to 10^{-4}. 0.1 mL aliquots of each undiluted and diluted specimen will be pipetted onto the surface of duplicate plates, containing Trypticase Soy Agar with polysorbate (Tween) 80. The aliquots will be evenly spread on the surface of the plate with a sterilized bent glass rod. The media for these analyses are shown in Appendix F.

Plated samples will be incubated aerobically for 18 - 24 hours at $35 \pm 2°C$. The CFU's of test bacteria will be counted at the end of the incubation period. In general, the number of CFU's per sample will be determined by taking the average of the counts from the plates which are in the range of ≥ 25 to ≤ 250 CFU's. If there are no plates with counts within this range, the following rules will be used to determine which counts will be used for the obtaining the number of CFU's for that specimen:

1. If all of the counts are below the prescribed range, the numbers below 25 from the undiluted plates will be used.
2. If the counts from the highest dilution are > 250, the numbers, obtained from using the estimated counting procedure described in Appendix F, will be used.

The number of CFU's for each dilution counted will be recorded on Source Document 2.

V. Study Material and Instructions

A. Study Materials

All test products will be sent by the Sponsor to the clinical site prior to study initiation.

Each treatment product will be identified with the appropriate label (Appendix D) affixed to the outside of each container.

B. Shipping of Study Materials

The quantity of all materials, including test products and study supplies shipped to and returned from the clinical site, will be documented on the Shipping and Receiving Form (Source Document 1). The products will be packed into one or more cartons labeled with:

1. the study number;
2. distributor statement (i.e., "Distributed by Hill Top Research, Inc. with the test facility's full address and phone number); and
3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator will insure that all test products, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Jan Englehart

VI. Other Study Documentation and Requirements

A. Adverse Event and Intercurrent Event Reporting

Should any unexpected or serious adverse event occur during the clinical study or as a result of application of the test organism to the skin of the subjects, the subject will be requested to return to the site to be examined by the Investigator. The Investigator will determine whether: (a) the adverse event is likely to be associated with product treatment or the study procedures; (b) the event warrants termination of participation; and (c) to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Jan Englehart, 513-626-1896 (work) or 513-385-9596 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in CRF 4. If treatment by a physician is necessary, this treatment will be documented on CRF 5.

B. Deviations from Protocol

Any deviations from the protocol that occur during execution and not previously agreed to by the Sponsor and Investigator will be documented. All changes in the protocol must be made in written amendments agreed upon by the Investigator and Sponsor. The amendments must be attached to the protocol on file.

C. Subject Termination and Completion

At the termination of the study, CRF 6 will be completed on all subjects. A concerted effort will be made to retain and follow all subjects in the study. Subjects, who terminate their own participation, prior to study closure, for any of the following reasons will also be documented in CRF 6.

a) Intolerance of the study procedures.
b) Intercurrent illness which interferes with the evaluation.
c) Noncompliance with the protocol.
d) Investigator decision to withdraw a subject from study.
e) Subjects, who are prescribed medication for an illness arising during the study, may be terminated on the basis of an intercurrent event. This event will be noted on the appropriate CRF's.
f) Subjects who decide to withdraw from the study for personal reasons.

D. Investigator Review

The Investigator will review all case report forms and will sign the Investigator Review Form (CRF 6) at study termination attesting to the completeness and accuracy of case report forms that pertain to their responsibilities.

VII. Statistical Analyses

Data will be analyzed using analysis of variance. Data will be analyzed according to a 3 x 3 factorial design. Factors will be treatment levels and subject. Additional terms to be included in the model provided there are sufficient degrees of freedom are side, arm site, and the side by site interaction. P-values ≤ 0.10 will be considered significant.

VIII. Ethical and Regulatory Requirements

A. Institutional Review Board (IRB) Review and Approval

Review by an IRB is required to conduct this study. A copy of the approval letter along with a list of the IRB members who acted on this protocol and a statement that the IRB is in compliance with current Good Clinical Practices (GCP) regulations will be provided to the Sponsor.

B. Subject Informed Consent

Prior to study initiation, all subjects will be informed as to the type of study, the procedures to be followed, the general nature of the products being tested, and any known or anticipated adverse reactions which might result from participation. Each subject must sign the written informed consent (Appendix A) before participating in this study. The informed consent will contain all the basic elements outlined in 21 CFR 50.25.

C. Study Monitoring

The Investigator will permit a representative of the Sponsor to make regular visits during the course of the study. During these visits, the Investigator will permit the Sponsor's Monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The Sponsor's Monitor will also be permitted to review and verify laboratory reports, case report forms, drug/test article supply and inventory records. Any comments/instructions made by the Sponsor's Monitor will be recorded in the Investigator's study file.

D. Protocol Revisions and Amendments

With the exception of emergency situations, no changes or deviations from this protocol will be permitted without documented approval from the Investigator and the Sponsor's Monitor.

All amendments to the final protocol will be initiated by the Sponsor. They will be consecutively numbered, describe any changes being made, and the reasons for them. All amendments will be signed and dated by the Sponsor and the Investigator, and the impact on the study noted. If the Investigator deviates from the agreed final protocol, the Sponsor's Monitor will be informed of the change as soon as possible by telephone.

E. Final Report

The Sponsor will generate a final report of clinical results.

F. Study Safety Statement

The requested testing meets the ethical requirements stipulated in the Procter & Gamble Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

G. Confidentiality

The obligations of the Investigator, Hill Top Research, Inc., regarding the confidential information on the antibacterial soap and all aspects of the study will be kept confidential according to the Laboratory Service agreement between Hill Top Research, Inc. and The Procter & Gamble Company.

IX. References

1. Williamson, P. and Kligman, A.M., A new method for the quantitative investigation of cutaneous bacteria. *J. Invest. Dermatol.*, 45:6 (1965) 498-503.

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Jan S. Englehart — Date: 11/18/97

Jan S. Englehart, B.S., ASCP, Clinical Research Associate
Clinical Research and Biometrics Department

APPROVED BY:

Ward L. Billhimer — Date: 11/18/97

Ward L. Billhimer, M.S., Senior Scientist
Clinical Research and Biometrics Department

Paula B. Neumann — Date: 11/18/97

Paula B. Neumann, Ph.D., Senior Scientist Biostatistician
Clinical Research and Biometrics Department

Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator for CRB-97-11-245-CD:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies including, but not limited to, those relating to Institutional Review Board (IRB), Informed Consent, and Good Clinical Practices.

I am aware that it is the responsibility of the Investigator to promptly report to the IRB all changes to the research activity and all unanticipated problems involving risk to human subjects. In addition, as Investigator, I am aware that a summary report must submitted to the IRB when the study is completed. These guidelines are in accordance with CFR 312.66. The Sponsor will be copied on all correspondence to and from the IRB.

Gayle K. Mulberry, M.S., Principal Investigator — Date: 11-19-97

Ann R. Brady, A.S., Sub-Investigator — Date: 11.19.97

XI. Attachments

The following Appendices, Case Report Forms, and Source Documents are included as attachments to the Final Protocol:

Appendices

A Written Informed Consent
B Subject's Instructions Following Study Completion
C Wash Procedure
D Product Labels
E List of Antibacterial/Antimicrobial Products
F Microbiological Media

Case Report Forms

1 Demographics/Dermatological/Medical History Form
2 Inclusion/Exclusion Form
3 Treatment Record
4 Adverse Event
5 Physician's Action Report Form
6 Subject Termination and Investigator Review Form

Source Documents

1 Shipping and Receiving of Study Material
2 Microbiology Worksheet - Enumeration of Organisms

Appendix A

HT# 97-5425-11
CRB-97-11-245-CD

WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B

HT# 97-5425-11
CRB-97-11-245-CD

SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Residual Effectiveness Screening Test". During this study, two (2) test sites on each of your forearms were inoculated with *Escherichia coli* bacteria. Although we do not expect you have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your forearms within the next 48 - 72 hours.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your arms during the next 48 - 72 hour period. If you notice the appearance of any pimples, blisters, or raised red itching bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:15 am - 5 pm) or at (513) 831-3354 after hours.

Thank you for your cooperation.

Appendix C

HT# 97-5425-11
CRB-97-11-245-CD

WASH PROCEDURE

Water temperature should be maintained at 95 -100° F.

The temperature should be checked and recorded before each wash.

Water flow should be 4 L/minute.

Time of each wash should be recorded.

A technician will wash each subject's arm.

The technician will wear gloves for this procedure, changing after each treatment area wash.

Wipe the template with 70% isopropyl alcohol after use.

Begin with the subject's **right** arm:

1. Using the template, mark two (2) 10 x 5 cm treatment areas (an upper and lower) on the subject's forearm.
2. The subject should wet the upper treatment site of their forearm under the running water.
3. Dispense 0.5 mL of the appropriate test product, from a 1 cc disposable syringe, onto the upper treatment site area.
4. The technician should wet their gloved hand under the running water.
5. The technician should carefully lather the test product with two (2) fingers in an up-and-down motion within the upper treatment site for forty-five (45) seconds.
6. The subject should rinse the upper treatment site avoiding crossover to the lower treatment site under the running water. Rinse for fifteen (15) seconds. **Do not rub!**
7. Repeat steps 1 to 6 for the lower treatment site.
8. Pat subjects' forearms dry using a paper towel. **Do not rub!**
9. Repeat steps 1 to 8 on the **left** forearm.

Appendix D

HT# 97-5425-11
CRB-97-11-245-CD

PRODUCT LABELS

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code A

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code B

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code C

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code D

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

Appendix D

HT# 97-5425-11
CRB-97-11-245-CD

PRODUCT LABELS

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code E

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code F

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code G

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code H

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing arms only.

Appendix D

HT# 97-5425-11
CRB-97-11-245-CD

PRODUCT LABELS

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code I

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code J

Study# CRB-97-11-245-CD
HT#97-5425-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

Appendix E

HT# 97-5425-11
CRB-97-11-245-CD

LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Anti-bacterial Dishwashing Liquids

Dawn
Joy
Palmolive
Dial

Appendix F

HT# 97-5425-11
CRB-97-11-245-CD

MICROBIOLOGICAL MEDIA

0.075M Phosphate Buffer Solution

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO4, 1.0 gram Triton X, 15.0 grams of polysorbate (Tween) 80, and 10.0 grams of Lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 with 0.1N NaOH. Dispense buffer in 100 mL quantities in bottles. Loosely cap bottles and sterilize in the autoclave at 121° C. Prepared buffer is checked for sterility and stored at 15 - 30°C for upto 30 days.

Trypticase Soy Broth (TSB)

Dissolve 30 grams in 1 liter of distilled or deionized water. If necessary, warm slightly to dissolve completely. Dispense broth in 9 mL quantities in sterile tubes. Sterilize at 121°C. Check for sterility. Prepared tubes are stored at 15 - 30°C and used within 30 days.

Trypticase Soy Agar with Polysorbate (Tween) 80

Suspend 40 grams in 1 liter of distilled or deionized water in a hear resistant flask. Heat to boiling with gentle mixing to dissolve completely. Add 15 grams of polysorbate (Tween) 80 and gently mix to dissolve completely. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45 - 50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Case Report Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
97-5425-11	Gayle K. Mulberry	Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male(1) ☐ Female(2)	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER	No	Yes	Don't Know
1. Psoriasis ?			
2. Eczema ?			
3. Skin Cancer ?			
4. Skin Allergies ? Please specify:			
5. Hives ?			

Does the Subject have any of the following (present and past)?

II. OTHER MEDICAL INFORMATION	No	Yes	Don't Know
1. Allergies ? Please specify.			
2. Hepatitis ?			
3. Heart and Vascular Disease?			
4. Liver Disease ?			
5. Kidney Disease ?			
6. Tuberculosis ?			
7. Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8. Cancer ?			
9. Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10. Organ transplant ?			
11. Any other condition not listed ? Please specify			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION	No	Yes	Don't Know
1. Antibiotics, oral or systemic ?			
2. Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3. Heart Medication ?			
4. Insulin ?			
5. Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: ___/___/___ mm dd yy

Case Report Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
97-5425-11	Gayle K. Mulberry	Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA

Check one YES	NO	Subject:
		1. Is 18 to 65 years ?
		2. Has signed informed consent ?
		3. Is healthy as evidenced by responses on CRF 1 ?
		4. Has forearms that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA

Check one YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility ?
			2. Has participated in any type of hand or arm wash study within the past 14 days ?
			3. Has cuts, lesions, or other skin disorders on the volar surface of either forearm ?
			4. Has soap, detergent, and/or perfume allergies ?
			5. Has eczema or psoriasis on their arm(s) ?
			6. Has taken systemic antibiotics or used topical antibiotics for any reason in the 3 weeks prior to the start of the test period ?
			7. Are currently using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos ?
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Case Report Forms 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Investigator's Signature:	Date: ___/___/___ mm dd yy

Case Report Form 3
TREATMENT RECORD

Study #	Hill Top Research, Inc.	Visit Code	Subject Initials	Permanent #:
97-5425-11	Gayle K. Mulberry	Test Period	____/____/____ F M L	

WASH RECORD						
Wash	Right Arm Test Sites		Left Arm Test Sites		Water Temp.	Initials / Date
	Upper (1)	Lower (2)	Upper (3)	Lower (4)		
Product Code						
1	am / pm	am / pm	am / pm	am / pm		/

INOCULATION, OCCLUSION, AND HARVESTING					
Right Arm	Site	Time Period	Inoculation and Occlusion Time	Harvesting Time	Initials / Date
	upper (1)		am / pm	am / pm	/
	lower (2)		am / pm	am / pm	/
Left Arm	Site	Time Period	Inoculation and Occlusion Time	Harvesting Time	Initials / Date
	upper (3)		am / pm	am / pm	/
	lower (4)		am / pm	am / pm	/

Microbiologist's Initials:	Investigator's Signature:	Date: ____/____/____ mm dd yy

Case Report Form 4

ADVERSE EVENT

Study #	Hill Top Research, Inc.	Date	Subject Initials	Permanent #:
97-5425-11	Gayle K. Mulberry	____/____/____ mm dd yy	____/____/____ F M L	

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician

☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm / dd / yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	

Investigator's Signature:	Recorded by:	Date ____/____/____ mm dd yy

Case Report Form 5

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.	Date	Subject Initials	Permanent #:
97-5425-11	Gayle K. Mulberry	____/____/____ mm dd yy	____/____/____ F M L	

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature

_____ Date

Case Report Form 6

SUBJECT TERMINATION AND INVESTIGATOR REVIEW FORM

Study #	Hill Top Research, Inc.	Visit Code	Subject Initials	Permanent #:
97-5425-11	Gayle K. Mulberry	End of Study	____/____/____ F M L	

Date Subject Entered the Study:	Date Subject Withdrew / Completed the Study:
____/____/____ mm dd yy	____/____/____ mm dd yy

Did subject drop out of study prior to completion? ☐ YES ☐ NO If yes, complete below:

Check reason for subject premature termination:

☐ 1 = Adverse Event (Documented on CRF 4)

☐ 2 = Intercurrent Event

☐ 3 = Lack of Compliance with Protocol Specify: _____

☐ 4 = Personal reasons (family problems, lack of transportation, etc.)

☐ 5 = No show, Lost to Follow-up

☐ 6 = Other Specify: _____

Comments: _____

_____

_____

MY SIGNATURE ON THIS PAGE CERTIFIES THAT I HAVE REVIEWED ALL OF THE DATA AND STATEMENTS SUBMITTED FOR THIS SUBJECT AND FIND THEM ACCURATE AND COMPLETE TO THE BEST OF MY KNOWLEDGE.

Investigator's Signature	Date
	____/____/____ mm dd yy

SOURCE DOCUMENT 1
CRB-97-11-245-CD
(HT# 97-5425-11)

SHIPPING & RECEIVING OF STUDY MATERIAL

MATERIALS SHIPPED	MATERIALS RECEIVED	MATERIALS RETURNED	MATERIALS RECEIVED
Date Shipped: _____ Time: _____	Date Received: _____	Date : _____ Time: _____	Date Received: _____
Test Site: _____	Time: _____	Test Site: _____	Time: _____
Method of Transport: _____	Test Site: _____	Method of Transport: _____	Test Site: _____

LISTING OF MATERIALS SHIPPED		MATERIALS RECEIVED	MATERIALS RETURNED	MATERIALS RETURNED
# of ITEMS	ITEM DESCRIPTION * * Include Batch no. in item description	4= OK D = LOST/DAMAGED NR = NOT RECEIVED	Indicate if items are returned or not returned	4= OK D = LOST/DAMAGED NR = NOT RECEIVED

Shipping Technician: _____	Receiving Technician: _____	Returning Technician: _____	Receiving Technician: _____
Date: _____	Date: _____	Date: _____	Date: _____

SOURCE DOCUMENT 2
HT# 97-5425-11
CRB-97-11-245-CD

MICROBIOLOGY WORKSHEET - ENUMERATION OF ORGANISMS

CFU COUNTS (TOTAL # ORGANISMS / mL)		
Date Plated:	**Date Counted:**	**Inoculum Count:**

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Laboratory Supervisor	Microbiologist	Date

PROTOCOL AMENDMENT Issue I 11/24/97

Residual Effectiveness Screening Test of Antibacterial Liquid Products against *E. coli*

Study Number: CRB-97-11-245-CD (HT 97-5425-11)

Purpose of the Amendment: **Changes to the Study Protocol**

CHANGE #1 **Clarification of the Title of the Protocol**

The title of the protocol will be modified to read as follows:

"Residual Effectiveness Screening Test of Liquid Products against *E. coli*"

The word "antibacterial" has been removed since all of the test products do not contain the antibacterial active ingredient.

CHANGE #2 **Clarification of the Objective of the Protocol**

The objective of the protocol will be modified to read as follows:

"The objective of this study is to evaluate the residual effectiveness of ten (10) liquid soap products against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection."

The words "containing an antibacterial active" have removed since all of the test products do not contain the antibacterial active ingredient.

For The Procter and Gamble Company:

J. S. Englehart

J. S. Englehart, B.S., Clinical Research Associate Date: 11/24/97

For Hill Top Research, Inc.:

Gayle K. Mulberry, M.S., Principal Investigator Date: 11/24/97

Ann R. Brady

Ann R. Brady, A.S., Sub-Investigator Date: 11.24.97

FINAL REPORT OF CLINICAL TEST RESULTS

From: P. B. Neumann, J. S. Englehart

Date: July 10, 1998

To: Study File for CRB-97-12-262-CD

Retention Limit: Until Superseded

Released: WLB 7/10/98

Subject: Residual Effectiveness Screening Test Results on B-22M Liquid Soap Formulations with Varying Levels of Salicylic Acid and Triclosan (TCS) and Liquid Ivory® against *E. coli* under Occluded and Unoccluded Conditions Hill Top Research, Inc., CRB-97-12-262-CD, HT 97-5461-11

Summary:

The results of this clinical study show that B-22M liquid soap formulation with 1.0% salicylic acid, code G, and B-22M liquid soap formulation with 1.0% salicylic acid and 1.0% TCS, code I, were significantly more effective than B-22M (no salicylic acid or TCS, code A) and Liquid Ivory, code J, at lowering the levels of *Escherichia coli* inoculated on the skin (p-value <0.10) under both occluded and unocludded conditions. Treatment and occlusion status were highly significant factors, their interaction was not.

The results are summarized in the attached tables.

Objective:

The objective of this study was to evaluate the residual effectiveness of four (4) liquid soap products against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection.

Test Products:

Code	Test Product	Active Ingredient	TSIN
A	B-22M	none	BI0060-108
G	B-22M, 1.0% salicylic acid	none	BI0060-092
I	B-22M, 1.0% salicylic acid	1.0% TCS	BI0060-096
J	Liquid Ivory Soap	none	BI0060-126

Study Design:

This study was conducted at Hill Top Research, Inc. in Miamiville, Ohio on December 2, 1997. This was a randomized, split forearm wash study to evaluate the residual antibacterial effectiveness of four (4) liquid products. Twenty (20) male and female subjects, ages 18 through 65 years old, who did not regularly use antibacterial soap, medicated lotion or cream, and/or antidandruff shampoo were enrolled to evaluate the products under both occluded and unoccluded conditions. For the test procedure, each of the subject's forearms was divided into an upper and lower treatment area, for a total of four (4) treatment areas per subject. Each treatment area was washed one (1) time for forty-five (45) seconds. Within five (5) minutes after the wash with the test products was completed, a 3.0 cm circular test site was marked-off in each area. Each circular site was then inoculated with 10 µL of a 24 hour broth culture of *E. coli* grown in Trypticase Soy Broth (TSB). According to a randomization, half of the test sites were occluded with a 24 mm Hill Top Chamber® that was taped to the skin with Durapore® tape. The other half of the test sites remained

Study Design: ***(continued)***

unoccluded. Ten (10) minutes after innoculation, the surviving organisms were harvested from each test site using the Williamson-Kligman scrub technique. The specimens from each site were plated on Trypticase Soy Agar with polysorbate (Tween) 80 and incubated for 18 - 24 hours at 35 ±2°C. The colony forming units (CFU's) of *E. coli* were counted at the end of the incubation period to determine the number of surviving organisms at each of the treated sites.

Data Analysis:

The surviving colony forming units (CFU's) of bacteria for each subject were enumerated. The numbers of bacteria were converted to base 10 logarithms. The $\log_{10}$ CFU counts were compared using analysis of variance techniques according to a 4 x 2 factorial design with factors of treatment, occlusion and subject, adjusting for subject to subject variability, side (right vs. left) variability, site (upper vs. lower) variability, and site to side variability, to estimate which of the test products had the greatest activity. P-values ≤ 0.10 were considered statistically significant.

Subject Accountability:

Twenty (20) subjects were enrolled and completed this study.

Adverse Events:

None reported.

Submitted by:

Paula B. Neumann

Paula B. Neumann

Jan S. Englehart

Jan S. Englehart

Treatments:
A = B22M
G = B22M, 1% Salicylic Acid
I = B22M, 1% Salicylic Acid, 1% TCS
J = Liquid Ivory Soap

Conclusions:

Treatment and occlusion status were highly significant factors. The interaction between these terms was not significant.

Significantly higher lsmean organism counts (*E. coli*) were detected with occlusion (p-value = 0.0003).

Liquid Ivory Soap sites had higher organism counts than either B22M with 1% salicylic acid or B22m with 1% salicylic acid & 1% TCS at p-values < 0.10.

B22M sites had higher organism counts than B22M with both salicylic acid and TCS (p-value = 0.04).

Occlude	Treatment	N	Mean	Std. Dev.
No	A	10	4.8	0.320
No	G	9	4.5	0.489
No	I	9	4.2	0.209
No	J	10	5.0	0.159
Yes	A	10	5.1	0.630
Yes	G	9	4.9	0.569
Yes	I	9	4.7	0.795
Yes	J	10	5.4	0.594

Occlude	LSMean	Std. Error	
No	4.64	0.074	p-value = 0.0003
Yes	5.06	0.074	

Treatment	LSMean	Std. Error		Pairwise p-values A	G	I	J
A	4.9	0.124	A	.	0.4383	0.0379	0.2443
G	4.8	0.134	G	0.4383	.	0.1138	0.1049
I	4.5	0.134	I	0.0379	0.1138	.	0.0006
J	5.1	0.126	J	0.2443	0.1049	0.0006	.

Overall p-value=0.0072

Treatment	Occlude	LSMean	Std. Error	LSMean #	
A	No	4.8	0.161	1	
A	Yes	5.1	0.161	2	
G	No	4.6	0.173	3	
G	Yes	5.0	0.173	4	Overall p-value=0.8832
I	No	4.2	0.172	5	
I	Yes	4.8	0.172	6	
J	No	5.0	0.163	7	
J	Yes	5.4	0.163	8	

Pairwise p-values (Note: These are not valid as the overall p-value is not significant.)

i/j	1	2	3	4	5	6	7	8
1	.	0.1239	0.4729	0.3715	0.0333	0.9620	0.4449	0.0178
2	0.1239	.	0.0408	0.6374	0.0012	0.2009	0.5370	0.2961
3	0.4729	0.0408	.	0.0886	0.1139	0.5267	0.1891	0.0068
4	0.3715	0.6374	0.0886	.	0.0028	0.3683	0.9015	0.1794
5	0.0333	0.0012	0.1139	0.0028	.	0.0138	0.0027	0.0001
6	0.9620	0.2009	0.5267	0.3683	0.0138	.	0.4187	0.0175
7	0.4449	0.5370	0.1891	0.9015	0.0027	0.4187	.	0.0664
8	0.0178	0.2961	0.0068	0.1794	0.0001	0.0175	0.0664	.

P. B. Neumann

RESIDUAL EFFECTIVENESS SCREENING TEST OF ANTIBACTERIAL LIQUID PRODUCTS AGAINST *E. COLI* UNDER OCCLUDED AND UNOCCLUDED CONDITIONS

Study Number:	CRB-97-12-262-CD
Study Identification:	HT# 97-5461-11
Principal Investigator:	Gayle K. Mulberry, M.S.
Sub-Investigator	Ann R. Brady, A.S.
Clinical Test Site:	Hill Top Research, Inc. Main and Mill Streets Miamiville, Ohio 45147
Sponsor:	The Procter & Gamble Company Clinical Research and Biometrics Division Personal Cleansing Sector 11511 Reed Hartman Highway Cincinnati, Ohio 45241
Sponsor Representative:	Ward L. Billhimer, M.S.
Sponsor Statistician:	Paula B. Neumann, Ph.D.
Sponsor Toxicologists:	Paul F. Sterchele, Ph.D. J. David Innis, Ph.D.
Clinical Research Associates:	Jan S. Englehart, B.S., ASCP
Start Date:	December 2, 1997

Confidentiality: The obligations of the Investigator, regarding the confidential information on the antibacterial soap and all aspects of the study will be kept confidential according to the agreement with The Procter & Gamble Company.

I. Study Objective

The objective of this study is to evaluate the residual effectiveness of four (4) liquid soap products containing an antibacterial active against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection.

II. Study Summary

This is a randomized blinded clinical study that will evaluate the residual effectiveness of four (4) liquid soap products using a split forearm test design. It will consist of a one (1) day test period. Twenty (20) male and female subjects, age 18 to 65 years, who do not regularly use antibacterial/antimicrobial soaps, medicated lotions and creams, and/or anti-dandruff shampoos will be enrolled into the study. During this study, twenty (20) subjects will be used to evaluate four (4) test products under both occluded and unoccluded conditions.

On the day of the test, subjects will report to the clinical test facility. Each of the subjects' forearms will be divided into an upper and lower treatment area for a total of four (4) treatment areas. Subjects will have each of their forearms washed by a laboratory technician with the test products according to a randomization.

Following treatment with the test products, a test site will be marked off in the center of each treatment area on the forearms. Each of the four (4) test sites will be inoculated with a known amount of *Escherichia coli* (ATCC 11229) grown in Trypticase Soy Broth (TSB). According to a randomization, half of the test sites will then be occluded with a Hill Top Chamber®. The other half of the test sites will remain unoccluded. After ten (10) minutes, the bacteria on the skin will be harvested using a scrub technique [1]. Each sample of harvested bacteria will be diluted, plated, and incubated. Following incubation, the number of surviving colony forming units (CFU's) for each site will be determined.

III. Study Population

Subjects will be screened for their eligibility to participate based upon information provided in the Demographics/Dermatological/Medical History Form [Case Report Form (CRF) 1]. Only subjects meeting the inclusion/exclusion criteria, outlined in CRF 2, will be allowed to participate in the study. If a subject is admitted to this study in apparent violation of any of the above criteria, the reason(s) for admission will be noted by the Investigator or his designee.

A. Subject Inclusion Criteria

Subjects are eligible for enrollment if they:

1. Are a male or female, age 18 to 65 years;
2. Have signed the Informed Consent (Appendix A);
3. Are in good health, as evidenced by response to the Demographics/ Dermatological/Medical History Form (CRF 1);
4. Have forearms that are free of dermatoses, cuts, lesions, and other skin disorders; and
5. Are willing to comply with all study protocol requirements.

B. Subject Exclusion Criteria

A subject cannot be enrolled in the study if they:

1. Are currently participating in another clinical study at this or any other facility;
2. Have participated in any type of hand or arm wash study within the past 14 days;
3. Have cuts, scratches, or a rash on the volar surface of either forearm;
4. Have soap, detergent, and/or perfume allergies;
5. Have eczema or psoriasis on their arm(s);
6. Have taken systemic antibiotics or used topical antibiotics for any reason in the three (3) weeks prior to the start of the study;
7. Are currently using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos;
8. Are currently pregnant;
9. Are currently lactating;
10. Have been medically diagnosed as having a medical condition which would preclude participation such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive); and/or
11. Have any other medical condition, which in the opinion of the Investigator would preclude participation.

IV. Study Design and Procedures

A. Randomization

The Sponsor will generate the study randomization for the assignment of treatment products. In addition, a randomization will be generated to indicate which test sites will be occluded and which sites will remain unoccluded. Subjects will be assigned to a treatment number which will become their permanent subject identification number. All subjects and site personnel, including the Investigator, will remain blinded to product identities.

B. Study Schedule

On the day of the test, prospective subjects will visit the test facility to complete a written informed consent, (Appendix A), the Demographics/Dermatological/ Medical History Form (CRF 1), and the Inclusion/Exclusion Form (CRF 2). Subjects who meet the study criteria, will be randomly assigned to a treatment regimen. Two (2) treatment areas, upper and lower, will be marked off on each arm. A lab technician will wash each of the treatment areas with one (1) of the test products according to the procedure described in Appendix C. After the wash with the test products is completed, a test site will be marked-off in the center of each treatment area on the subjects' forearms. These sites will be inoculated, occluded, and harvested according to the procedures described below.

To ensure that any delayed adverse events, primarily skin infections, are reported to the study Investigator, all test subjects will be given a copy of Subjects' Instructions Following Study Completion (Appendix B) before leaving the clinical test facility after they have completed the study. This sheet will instruct the subjects to examine their forearms 48 - 72 hours after completion of the study for the presence of pimples, blisters, or raised red itching bumps surrounded by erythema and/or

edema that may be indicative of a skin infection. Subjects, who notice any of these lesions, will be instructed to call the clinical test site.

C. Wash with the Test Products

Two (2) 10 x 5 cm treatment areas (upper and lower) will be marked off on each subject's forearms using a template. Each of the four (4) treatment areas on the subjects' forearms will be washed by a laboratory technician according to the procedure outlined in Wash Procedure, Appendix C. Each treatment area will be washed one (1) time with the appropriate test product. A record of the subject washes will be kept on CRF 3. In general, the following should be noted: water temperature should be closely monitored and maintained at 95-100°F. The water temperature should be recorded. Wash time should be recorded at the start of washing.

D. Microbial Inoculation

Within five (5) minutes after the wash with the test products is completed, one (1) circular test site will be marked-off in each treatment area of the subject's forearms. These circular sites will be spaced in the center of each treatment area of the forearm. They will be made by pressing a 3.0 cm diameter glass cylinder, inked with a stamp pad, against the skin.

All test sites on both arms will be inoculated with *E. coli* (ATCC 11229) that has been grown in Trypticase Soy Broth (TSB). To determine the actual number of CFU/mL at the time of inoculation, the broth culture to be used for inoculation will be plated.

Using an Eppendorf® pipette, the skin area delineated by the cylinder will be inoculated with 10 µL of the bacterial culture to obtain 10^6 to 10^7 colony forming units (CFU's) of *E. coli*. A sterile, disposable, inoculating loop will be used to evenly spread the inoculum within the center of the test site while remaining 4 to 5 mm from the marked edge. Inoculation of each site will be documented on CRF 3.

E. Occlusion of the Test Sites

According to a randomization, half of the inoculated test sites will be immediately occluded by covering with a small plastic bowl (25 mm Hill Top Chamber® with pad removed) that will be secured to the skin with an adhesive dressing (Durapore®, 3M). The time of occlusion will be recorded on CRF 3. *The remaining half will not be occluded.* Time following inoculation should be recorded on CRF 3.

Following inoculation, all subjects will be instructed to rest their arms on a table, with the volar side of their forearms in an upward position, for approximately ten (10) minutes.

F. Harvesting of the Surviving *E. coli* Organisms

All inoculated sites will be harvested for surviving organisms at approximately ten (10) minutes after inoculation. The time of harvesting will be recorded on CRF 3.

The following procedure will be used for harvesting:

1. A hollow glass cylinder 2.2 cm in diameter will be positioned in the middle area of the test site avoiding contact with the ink-stamped edge.
2. 1.0 mL of phosphate-buffered 0.1% Triton X-100 detergent (pH 7.9), with suitable neutralizers, will be pipetted into the cylinder.

3. The skin inside the cylinder will be massaged for 60 seconds with a Teflon policeman.
4. The fluid will be removed by pipetting it into an empty sterile culture tube.
5. Another 1.0 mL of buffered detergent will be added for a second 30 second scrub.
6. The fluid from the second scrub will be removed and pooled with the fluid from the first scrub.

G. Disinfection of the Test Sites

After each test site is harvested, it will be disinfected with 70% isopropyl alcohol. When the harvesting of the last test site is completed, both forearms will be washed for approximately thirty (30) seconds with Hibiclens® (4% chlorhexidine gluconate). After the arms have been washed with Hibiclens®, a small amount of Polysporin® antibiotic ointment will be applied to each test site.

H. Plating and Incubation of the Organisms

Specimens from each of the four (4) sites will be plated within four (4) hours after harvesting. For plating, they will be serially diluted in half-strength (0.0375 M) buffer in ten-fold dilutions to 10^{-4}. 0.1 mL aliquots of each undiluted and diluted specimen will be pipetted onto the surface of duplicate plates, containing Trypticase Soy Agar with polysorbate (Tween) 80. The aliquots will be evenly spread on the surface of the plate with a sterilized bent glass rod. The media for these analyses are shown in Appendix F.

Plated samples will be incubated aerobically for 18 - 24 hours at 35 $\pm$ 2°C. The CFU's of test bacteria will be counted at the end of the incubation period. In general, the number of CFU's per sample will be determined by taking the average of the counts from the plates which are in the range of $\geq$ 25 to $\leq$ 250 CFU's. If there are no plates with counts within this range, the following rules will be used to determine which counts will be used for the obtaining the number of CFU's for that specimen:

1. If all of the counts are below the prescribed range, the numbers below 25 from the undiluted plates will be used.
2. If the counts from the highest dilution are > 250, the numbers, obtained from using the estimated counting procedure described in Appendix F, will be used.

The number of CFU's for each dilution counted will be recorded on Source Document 2.

V. Study Material and Instructions

A. Study Materials

All test products will be sent by the Sponsor to the clinical site prior to study initiation.

Each treatment product will be identified with the appropriate label (Appendix D) affixed to the outside of each container.

B. Shipping of Study Materials

The quantity of all materials, including test products and study supplies shipped to and returned from the clinical site, will be documented on the Shipping and Receiving Form (Source Document 1). The products will be packed into one or more cartons labeled with:

1. the study number;

2. distributor statement (i.e., "Distributed by Hill Top Research, Inc. with the test facility's full address and phone number); and

3. any applicable safety and handling procedures.

C. Return of Study Materials

Upon completion of the study, the Investigator will insure that all test products, whether completely used, partially used, or unused will be returned to the Sponsor at the following address:

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, Ohio 45241
Attn.: Jan Englehart

VI. Other Study Documentation and Requirements

A. Adverse Event and Intercurrent Event Reporting

Should any unexpected or serious adverse event occur during the clinical study or as a result of application of the test organism to the skin of the subjects, the subject will be requested to return to the site to be examined by the Investigator. The Investigator will determine whether: (a) the adverse event is likely to be associated with product treatment or the study procedures; (b) the event warrants termination of participation; and (c) to prescribe treatment, if necessary. The Investigator will notify the Sponsor representatives, Ward Billhimer, 513-626-1926 (work) or 513-831-8163 (home) or Jan Englehart, 513-626-1896 (work) or 513-385-9596 (home).

Each subject will need to be followed until the resolution of any adverse event. Information pertaining to the presenting signs, working diagnosis, assessment of the relationship of the adverse event to the product treatment, results of the follow-up visits and any prescribed treatment, will be documented in CRF 4. If treatment by a physician is necessary, this treatment will be documented on CRF 5.

B. Deviations from Protocol

Any deviations from the protocol that occur during execution and not previously agreed to by the Sponsor and Investigator will be documented. All changes in the protocol must be made in written amendments agreed upon by the Investigator and Sponsor. The amendments must be attached to the protocol on file.

C. Subject Termination and Completion

At the termination of the study, CRF 6 will be completed on all subjects. A concerted effort will be made to retain and follow all subjects in the study. Subjects, who terminate their own participation, prior to study closure, for any of the following reasons will also be documented in CRF 6.

a) Intolerance of the study procedures.

b) Intercurrent illness which interferes with the evaluation.

c) Noncompliance with the protocol.

d) Investigator decision to withdraw a subject from study.

e) Subjects, who are prescribed medication for an illness arising during the study, may be terminated on the basis of an intercurrent event. This event will be

noted on the appropriate CRF's.

f) Subjects who decide to withdraw from the study for personal reasons.

D. Investigator Review

The Investigator will review all case report forms and will sign the Investigator Review Form (CRF 6) at study termination attesting to the completeness and accuracy of case report forms that pertain to their responsibilities.

VII. Statistical Analyses

Data will be analyzed using analysis of variance. Data will be analyzed according to a 4 x 2 factorial design with factors of treatment, occlusion, and subject. Additional terms to be included in the model provided there are sufficient degrees of freedom are side, arm site, and the side by site interaction. P-values ≤ 0.10 will be considered significant.

VIII. Ethical and Regulatory Requirements

A. Institutional Review Board (IRB) Review and Approval

Review by an IRB is required to conduct this study. A copy of the approval letter along with a list of the IRB members who acted on this protocol and a statement that the IRB is in compliance with current Good Clinical Practices (GCP) regulations will be provided to the Sponsor.

B. Subject Informed Consent

Prior to study initiation, all subjects will be informed as to the type of study, the procedures to be followed, the general nature of the products being tested, and any known or anticipated adverse reactions which might result from participation. Each subject must sign the written informed consent (Appendix A) before participating in this study. The informed consent will contain all the basic elements outlined in 21 CFR 50.25.

C. Study Monitoring

The Investigator will permit a representative of the Sponsor to make regular visits during the course of the study. During these visits, the Investigator will permit the Sponsor's Monitor to inspect all forms and corresponding study subject's records to verify adherence to the protocol. The Sponsor's Monitor will also be permitted to review and verify laboratory reports, case report forms, drug/test article supply and inventory records. Any comments/instructions made by the Sponsor's Monitor will be recorded in the Investigator's study file.

D. Protocol Revisions and Amendments

With the exception of emergency situations, no changes or deviations from this protocol will be permitted without documented approval from the Investigator and the Sponsor's Monitor.

All amendments to the final protocol will be initiated by the Sponsor. They will be consecutively numbered, describe any changes being made, and the reasons for them. All amendments will be signed and dated by the Sponsor and the Investigator, and the impact on the study noted. If the Investigator deviates from the agreed final protocol, the Sponsor's Monitor will be informed of the change as soon as possible by telephone.

E. Final Report

The Sponsor will generate a final report of clinical results.

F. Study Safety Statement

The requested testing meets the ethical requirements stipulated in the Procter & Gamble Policy for Research Involving Human Subjects. Appropriate safety testing has been completed and risk assessments justify the placement of the test products in this study at these concentrations (levels of exposure).

G. Confidentiality

The obligations of the Investigator, Hill Top Research, Inc., regarding the confidential information on the antibacterial soap and all aspects of the study will be kept confidential according to the Laboratory Service agreement between Hill Top Research, Inc. and The Procter & Gamble Company.

IX. References

1. Williamson, P. and Kligman, A.M., A new method for the quantitative investigation of cutaneous bacteria. *J. Invest. Dermatol.*, 45:6 (1965) 498-503.

X. Sponsor and Investigator Concurrence

For The Procter and Gamble Company

PREPARED BY:

Jan S. Englehart

Jan S. Englehart, B.S., ASCP, Clinical Research Associate
Clinical Research and Biometrics Department

Date: 11/18/97

APPROVED BY:

Ward L. Billhimer

Ward L. Billhimer, M.S., Senior Scientist
Clinical Research and Biometrics Department

Date: 11/18/97

Paula B. Neumann, Ph.D., Senior Scientist Biostatistician
Clinical Research and Biometrics Department

Date: 11/18/97

Agreed and Accepted by Hill Top Research, Inc. and the Study Investigator for CRB-97-12-262-CD:

I certify that I have reviewed and approved the protocol, informed consent form, and other associated documents and agree to abide by their terms. In addition, I agree to conduct this clinical study in compliance with federal, state and local government regulations, guidelines and standards applicable to such studies including, but not limited to, those relating to Institutional Review Board (IRB), Informed Consent, and Good Clinical Practices.

I am aware that it is the responsibility of the Investigator to promptly report to the IRB all changes to the research activity and all unanticipated problems involving risk to human subjects. In addition, as Investigator, I am aware that a summary report must submitted to the IRB when the study is completed. These guidelines are in accordance with CFR 312.66. The Sponsor will be copied on all correspondence to and from the IRB.

Gayle K. Mulberry, M.S., Principal Investigator — Date: 11-19-97

Ann R. Brady, A.S., Sub-Investigator — Date: 11.19.97

XI. Attachments

The following Appendices, Case Report Forms, and Source Documents are included as attachments to the Final Protocol:

Appendices

A	Written Informed Consent
B	Subject's Instructions Following Study Completion
C	Wash Procedure
D	Product Labels
E	List of Antibacterial/Antimicrobial Products
F	Microbiological Media

Case Report Forms

1	Demographics/Dermatological/Medical History Form
2	Inclusion/Exclusion Form
3	Treatment Record
4	Adverse Event
5	Physician's Action Report Form
6	Subject Termination and Investigator Review Form

Source Documents

1	Shipping and Receiving of Study Material
2	Microbiology Worksheet - Enumeration of Organisms

Appendix A

HT# 97-5461-11
CRB-97-12-262-CD

WRITTEN INFORMED CONSENT

To be provided by the clinical site.

Appendix B

HT# 97-5461-11
CRB-97-12-262-CD

SUBJECT'S INSTRUCTIONS FOLLOWING STUDY COMPLETION

You have just completed participation in a clinical study, "Residual Effectiveness Screening Test". During this study, two (2) test sites on each of your forearms were inoculated with *Escherichia coli* bacteria. Although we do not expect you have any adverse experience as a result of participation in this study, there is a remote possibility that an infection may develop on your forearms within the next 48 - 72 hours.

To determine whether you have developed an infection from the test bacteria, we would like you to examine your arms during the next 48 - 72 hour period. If you notice the appearance of any pimples, blisters, or raised red itching bumps surrounded by redness and/or swelling, please contact Gayle Mulberry or Ann Brady at (513) 831-3114 during normal business hours (8:15 am - 5 pm) or at (513) 831-3354 after hours.

Thank you for your cooperation.

Appendix C

HT# 97-5461-11
CRB-97-12-262-CD

WASH PROCEDURE

Water temperature should be maintained at 95 -100° F.

The temperature should be checked and recorded before each wash.

Water flow should be 4 L/minute.

Time of each wash should be recorded.

A technician will wash each subject's arm.

The technician will wear gloves for this procedure, changing after each treatment area wash.

Wipe the template with 70% isopropyl alcohol after use.

Begin with the subject's **right** arm:

1. Using the template, mark two (2) 10 x 5 cm treatment areas (an upper and lower) on the subject's forearm.
2. The subject should wet the upper treatment site of their forearm under the running water.
3. Dispense 0.5 mL of the appropriate test product, from a 1 cc disposable syringe, onto the upper treatment site area.
4. The technician should wet their gloved hand under the running water.
5. The technician should carefully lather the test product with two (2) fingers in an up-and-down motion within the upper treatment site for forty-five (45) seconds.
6. The subject should rinse the upper treatment site avoiding crossover to the lower treatment site under the running water. Rinse for fifteen (15) seconds. **Do not rub!**
7. Repeat steps 1 to 6 for the lower treatment site.
8. Pat subjects' forearms dry using a paper towel. **Do not rub!**
9. Repeat steps 1 to 8 on the **left** forearm.

Appendix D

HT# 97-5461-11
CRB-97-12-262-CD

PRODUCT LABELS

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code A

Study# CRB-97-12-262-CD
HT#97-5461-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code G

Study# CRB-97-12-262-CD
HT#97-5461-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code I

Study# CRB-97-12-262-CD
HT#97-5461-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

ANTIBACTERIAL
LIQUID SOAP PRODUCT
Product Code J

Study# CRB-97-12-262-CD
HT#97-5461-11
Net Contents: 100 g
Distributed by:
Hill Top Research
Main and Mill Streets
Miamiville, Ohio 45147
(513) 831-3354
May Contain: Triclosan (TCS)
Exp. Date: 1/1/98

Use as directed for washing
and arms only.

Appendix E

HT# 97-5461-11
CRB-97-12-262-CD

LIST OF ANTIBACTERIAL / ANTIMICROBIAL PRODUCTS

Medicated Acne Cleansers

Benzac W Wash 5
Desuam-X 5 Wash
Benzac W Wash 10
Desquam-X 10m Wash
Fostex 10% BPO Wash
Oxy 10 Wash
Propa P.H. Liquid Acne Soap
PanOxyl 5
Fostex 10% BPO
PanOxyl 10
Clearasil Antibacterial Soap
Sastid Plain Therapeutic Shampoo and Acne Wash
Oxy Clean Soap
Fostex Medicated Cleansing Bar
Salicylic Acid and Sulfur Soap
Sulfur Soap

Antidandruff Shampoos

Head and Shoulders (all formulas)
Selsun Blue (all formulas)
Pert Plus for Dandruff
Suave for dandruff
Neutrogena T-gel
Neutrogena T-sal
Scalpacin
Tegrin
Any antidandruff shampoo

Anti-bacterial Soaps

Safeguard bar and liquid
Lever 2000 bar and liquid
Irish Spring bar
Dial bar and liquid
Softsoap Antibacterial Soap

Antibiotic Ointments and Creams

Bacitracin
Polysporin
J & J First Aid Cream
Neomycin

Anti-bacterial Dishwashing Liquids

Dawn
Joy
Palmolive
Dial

Appendix F

HT# 97-5461-11
CRB-97-12-262-CD

MICROBIOLOGICAL MEDIA

0.075M Phosphate Buffer Solution

Weigh 0.4 grams of KH_2PO_4, 10.1 grams of Na_2HPO4, 1.0 gram Triton X, 15.0 grams of polysorbate (Tween) 80, and 10.0 grams of Lecithin. Dissolve in 1 liter of distilled or deionized water. Adjust to pH 7.9 with 0.1N NaOH. Dispense buffer in 100 mL quantities in bottles. Loosely cap bottles and sterilize in the autoclave at 121° C. Prepared buffer is checked for sterility and stored at 15 - 30°C for upto 30 days.

Trypticase Soy Broth (TSB)

Dissolve 30 grams in 1 liter of distilled or deionized water. If necessary, warm slightly to dissolve completely. Dispense broth in 9 mL quantities in sterile tubes. Sterilize at 121°C. Check for sterility. Prepared tubes are stored at 15 - 30°C and used within 30 days.

Trypticase Soy Agar with Polysorbate (Tween) 80

Suspend 40 grams in 1 liter of distilled or deionized water in a hear resistant flask. Heat to boiling with gentle mixing to dissolve completely. Add 15 grams of polysorbate (Tween) 80 and gently mix to dissolve completely. Loosely cap flask and sterilize in the autoclave at 121°C. Cool to 45 - 50°C in a water bath. Pour in sterile 15 x 100 mm Petri dishes. Allow to cool and solidify on a level flat surface. Check for sterility. Prepared plates are stored at 2 - 8°C and used within 30 days.

Estimated Plate Count Procedure

Do not record counts on crowded plates from the highest dilution as too numerous to count (TNTC). If the number of colonies per plate exceeds 250, count colonies in those portions of the plate that are representative of colony distribution and calculate the Estimated Standard Plate Count (ESPC) from these counts. The ESPC will be determined utilizing the grid embossed area on the lighted surface of the colony counter. Each large square on the grid is 1 cm^2. If there are fewer than 10 colonies per square centimeter, count colonies in 12 squares, selecting, if representative, six consecutive squares horizontally across the plate and six consecutive squares at right angles, being careful not to count a square more than once. When there are more than 10 colonies per square centimeter, count colonies in four such representative portions. In both instances, multiply the average found per square centimeter by the area of the plate used to determine the estimated number of colonies per plate.

If the total number of CFU's have been estimated according to the procedure described above, ESPC (Estimated Standard Plate Count) should be recorded following the value.

Note: If the highest dilution plated contains >250 CFU's and a count ≤300 CFU's has been previously determined, that value may be reported. It will not be necessary to estimate the total CFU's on a plate containing >250 CFU's using the above procedure. Plates containing the highest dilution of test specimen plated and the CFU counts are greater than 300, then the above procedure should be used to determine the total CFU count.

Case Report Form 1

DEMOGRAPHICS/DERMATOLOGICAL/MEDICAL HISTORY FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
97-5461-11	Gayle K. Mulberry	Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

Gender: ☐ Male(1) ☐ Female(2)	Age: _____ Years

Does the subject have any of the following at the treatment sites?

I. DERMATOLOGIC DISORDER		No	Yes	Don't Know
1.	Psoriasis ?			
2.	Eczema ?			
3.	Skin Cancer ?			
4.	Skin Allergies ? Please specify:			
5.	Hives ?			

Does the Subject have any of the following (present and past)?

II. OTHER MEDICAL INFORMATION		No	Yes	Don't Know
1.	Allergies ? Please specify.			
2.	Hepatitis ?			
3.	Heart and Vascular Disease?			
4.	Liver Disease ?			
5.	Kidney Disease ?			
6.	Tuberculosis ?			
7.	Diabetes ? Controlled? Diet [ ] Oral [ ] Insulin [ ]			
8.	Cancer ?			
9.	Auto-immune disease (Lupus erythematosus, thyroiditis, AIDS, etc.) ?			
10.	Organ transplant ?			
11.	Any other condition not listed ? Please specify:			

Is the subject taking any medication? If yes, please specify below:

III. MEDICATION		No	Yes	Don't Know
1.	Antibiotics, oral or systemic ?			
2.	Cortisone, Steroids, ACTH, Anti-reaction Drugs ?			
3.	Heart Medication ?			
4.	Insulin ?			
5.	Other ?			

Comments:

Based on the above medical history, the subject is: ☐ **Qualified** or ☐ **Not qualified** for the study.

Interviewer's Signature:	Date: _____/_____/_____ mm dd yy

Case Report Form 2
INCLUSION / EXCLUSION FORM

Study #	Hill Top Research, Inc.	Visit Code	Date	Subject Initials	Subject Screen #
97-5461-11	Gayle K. Mulberry	Subject Qualification	___/___/___ mm dd yy	___/___/___ F M L	Permanent #:

INCLUSION CRITERIA		
Check one YES	NO	Subject:
		1. Is 18 to 65 years ?
		2. Has signed informed consent ?
		3. Is healthy as evidenced by responses on CRF 1 ?
		4. Has forearms that are free of dermatoses, cuts, lesions, and other skin disorders ?
		5. Is willing to comply with all study protocol requirements ?

EXCLUSION CRITERIA			
Check one YES	NO	N/A	Subject:
			1. Is currently participating in another clinical study at this or any other facility ?
			2. Has participated in any type of hand or arm wash study within the past 14 days ?
			3. Has cuts, lesions, or other skin disorders on the volar surface of either forearm ?
			4. Has soap, detergent, and/or perfume allergies ?
			5. Has eczema or psoriasis on their arm(s) ?
			6. Has taken systemic antibiotics or used topical antibiotics for any reason in the 3 weeks prior to the start of the test period ?
			7. Are currently using antibacterial/antimicrobial soaps (liquids and/or bars), medicated lotions and creams, and/or anti-dandruff shampoos ?
Female	Female	Male	8. Is currently pregnant ? ☐ Yes ☐ No Of child-bearing potential: ☐ Yes ☐ No ☐ Surgically Sterile ☐ Post-menopausal If of child bearing potential - β-HCG Test Results: ☐ negative ☐ positive
Female	Female	Male	9. Is currently lactating?
			10. Has been medically diagnosed as having a medical condition such as: diabetes, hepatitis, an organ transplant, or AIDS (or HIV positive) ?
			11. Has another medical condition which in the opinion of the Investigator would preclude participation ?

Based upon dermatologic evaluation and the information contained in Case Report Forms 1 and 2, the subject is:

☐ **Qualified** ☐ **Not Qualified** for participation in this study.

Reasons for disqualification: _____

Investigator's Signature:	Date: ____/____/____ mm dd yy

Case Report Form 3
TREATMENT RECORD

Study #	Hill Top Research, Inc.	Visit Code	Subject Initials	Permanent #:
97-5461-11	Gayle K. Mulberry	Test Period	____/____/____ F M L	

WASH RECORD						
Wash	Right Arm Test Sites		Left Arm Test Sites		Water Temp.	Initials / Date
	Upper (1)	Lower (2)	Upper (3)	Lower (4)		
Product Code						
1	am / pm	am / pm	am / pm	am / pm		/

INOCULATION, OCCLUSION, AND HARVESTING						
Right Arm	Site	Time Period	Inoculation Time	Occluded	Harvesting Time	Initials / Date
	upper (1)		am / pm	yes / no	am / pm	/
	lower (2)		am / pm	yes / no	am / pm	/
Left Arm	Site	Time Period	Inoculation Time	Occluded	Harvesting Time	Initials / Date
	upper (3)		am / pm	yes / no	am / pm	/
	lower (4)		am / pm	yes / no	am / pm	/

Microbiologist's Initials:	Investigator's Signature:	Date: ____/____/____ mm dd yy

Case Report Form 4

ADVERSE EVENT

Study #	Hill Top Research, Inc.	Date	Subject Initials	Permanent #:
97-5461-11	Gayle K. Mulberry	____/____/____ mm dd yy	____/____/____ F M L	

Was reaction related to treatment? ☐ Not related ☐ Possibly related ☐ Definitely related ☐ Other (explain)

Did subject take any medication during the study period? ☐ YES ☐ NO If yes, complete section below.

Date of Onset: _____ Date Reported: _____ Date Resolved: _____

Describe event: _____

_____

_____

_____

Action Taken: ☐ None ☐ Continued on study ☐ Withdrawn from the study ☐ Consulted physician

☐ Medication taken (Complete below) ☐ Hospitalized ☐ Other (explain)

Additional Comments:

FOLLOW - UP ACTION TAKEN

Date	Action Taken	Comments	Initials

CONCOMITANT MEDICATION TAKEN

Medication *(Oral or Systemic)*	Total Daily Dose	Start Date mm / dd / yy	Stop Date mm / dd / yy	Indication *(Reason for Taking)*
		/ /	/ /	
		/ /	/ /	
		/ /	/ /	

Investigator's Signature:	Recorded by:	Date ____/____/____ mm dd yy

Case Report Form 5

PHYSICIAN'S ACTION REPORTING FORM

Study #	Hill Top Research, Inc.	Date	Subject Initials	Permanent #:
97-5461-11	Gayle K. Mulberry	____/____/____ mm dd yy	____/____/____ F M L	

Date(s) of office visit(s): _____

Pertinent Medical History: (e.g., causes of similar reactions, known allergies, potential involvement of current medications or medical conditions)

_____

_____

Test Product Exposure:

Use Began On: _____ Date Used Ended on: _____ Date Number of Uses: _____

Clinical Observations: (Include date of onset and descriptions/severity/locations, etc.)

_____

_____

Impression: _____

_____

Treatment: _____

_____

Follow Up: _____

_____

Date Resolved: _____

Is condition related to use of the test products?

[ ] Probably related* [ ] Not Related* [ ] Unknown

Reasons: _____

_____ Physician's Signature

_____ Date

Case Report Form 6

SUBJECT TERMINATION AND INVESTIGATOR REVIEW FORM

Study #	Hill Top Research, Inc.	Visit Code	Subject Initials	Permanent #:
97-5461-11	Gayle K. Mulberry	End of Study	____/____/____ F M L	

Date Subject Entered the Study:	Date Subject Withdrew / Completed the Study:
____/____/____ mm dd yy	____/____/____ mm dd yy

Did subject drop out of study prior to completion? ☐ YES ☐ NO If yes, complete below:

Check reason for subject premature termination:

☐ 1 = Adverse Event (Documented on CRF 4)

☐ 2 = Intercurrent Event

☐ 3 = Lack of Compliance with Protocol Specify: _____

☐ 4 = Personal reasons (family problems, lack of transportation, etc.)

☐ 5 = No show, Lost to Follow-up

☐ 6 = Other Specify: _____

Comments: _____

_____

_____

MY SIGNATURE ON THIS PAGE CERTIFIES THAT I HAVE REVIEWED ALL OF THE DATA AND STATEMENTS SUBMITTED FOR THIS SUBJECT AND FIND THEM ACCURATE AND COMPLETE TO THE BEST OF MY KNOWLEDGE.

Investigator's Signature	Date ____/____/____ mm dd yy

SOURCE DOCUMENT 1
CRB-97-12-262-CD
(HT# 97-5461-11)

SHIPPING & RECEIVING OF STUDY MATERIAL

MATERIALS SHIPPED	MATERIALS RECEIVED	MATERIALS RETURNED	MATERIALS RECEIVED
Date Shipped: _____ Time: _____	Date Received: _____	Date : _____ Time: _____	Date Received: _____
Test Site: _____	Time: _____	Test Site: _____	Time: _____
Method of Transport: _____	Test Site: _____	Method of Transport: _____	Test Site: _____

LISTING OF MATERIALS SHIPPED		MATERIALS RECEIVED	MATERIALS RETURNED	MATERIALS RETURNED
# of ITEMS	ITEM DESCRIPTION * * Include Batch no. in item description	4= OK D = LOST/DAMAGED NR = NOT RECEIVED	Indicate if items are returned or not returned	4= OK D = LOST/DAMAGED NR = NOT RECEIVED

Shipping Technician: _____	Receiving Technician: _____	Returning Technician: _____	Receiving Technician: _____
Date: _____	Date: _____	Date: _____	Date: _____

SOURCE DOCUMENT 2
HT# 97-5461-11
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MICROBIOLOGY WORKSHEET - ENUMERATION OF ORGANISMS

CFU COUNTS (TOTAL # ORGANISMS / mL)

Date Plated:	Date Counted:	Inoculum Count:

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Subject No.	Test Site	Right Arm				Left Arm			
		1 *(upper)*		2 *(lower)*		3 *(upper)*		4 *(lower)*	
		Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2	Plate 1	Plate 2
	10^{-1}								
	10^{-2}								
	10^{-3}								
	10^{-4}								
	10^{-5}								

Laboratory Supervisor	Microbiologist	Date

PROTOCOL AMENDMENT Issue I 11/24/97

Residual Effectiveness Screening Test of Antibacterial Liquid Products against *E. coli* under Occluded and Unoccluded Conditions

Study Number: **CRB-97-11-262-CD (HT 97-5461-11)**

Purpose of the Amendment: **Changes to the Study Protocol**

CHANGE #1 **Clarification of the Title of the Protocol**

The title of the protocol will be modified to read as follows:

> **"Residual Effectiveness Screening Test of Liquid Products against *E. coli* under Occluded and Unoccluded Conditions**

The word "antibacterial" has been removed since all of the test products do not contain the antibacterial active ingredient.

CHANGE #2 **Clarification of the Objective of the Protocol**

The objective of the protocol will be modified to read as follows:

> "The objective of this study is to evaluate the residual effectiveness of four (4) liquid soap products against potentially pathogenic bacteria (*Escherichia coli*, ATCC 11229) under simulated skin conditions which are considered optimal for bacterial growth, proliferation, and possible infection."

The words "containing an antibacterial active" have removed since all of the test products do not contain the antibacterial active ingredient.

For The Procter and Gamble Company:

J. S. Englehart

J. S. Englehart, B.S., Clinical Research Associate Date: 11/24/97

For Hill Top Research, Inc.:

Gayle K. Mulberry, M.S., Principal Investigator Date: 11/24/97

Ann R. Brady, A.S. Sub-Investigator Date: 11.24.97


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