DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Part 348

[Docket No. 78N-0301]

External Analgesic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph and Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) external analgesic drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by March 6, 1980 and reply comments by April 3, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on May 23, 1978, a report of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC external analgesic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it.

The Panel recommended classification of the ingredient methapyrilene hydrochloride in Category I for topical use as an external analgesic. Subsequent to this recommendation, studies, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animal and must be considered a potential human carcinogen. These data are on file in the office of the Hearing Clerk (address given above) under Docket No. 75N-0244. In June 1979, the agency initiated a recall of all oral and topical products containing methapyrilene. Products containing methapyrilene are considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. The Panel's report and proposed monograph, however, have not been changed to reflect these subsequent events.

FDA is aware of the recommendation to make low concentrations of hydrocortisone available for OTC use. Without addressing the merits of this recommendation, the agency merely wishes to point out that no final decision will be made without careful and thorough evaluation of all comments which are submitted in response to the publication of this recommendation. Any persons marketing such an OTC product prior to the publication in the **Federal Register** of a final monograph will do so at their own risk, as detailed in § 330.13 (21 CFR 330.13).

After reviewing all comments submitted in response to this proposal, FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC external analgesic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the panel and FDA have held as confidential all data and information concerning OTC external analgesic drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after January 3, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address given above).

Based upon the conclusions and recommendations of the Panel, the agency proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph, because the available data are insufficient (Category III) to classify such conditions either as Category I or Category II will be the subject of a later notice. The status of Category III conditions after publication of a final order is the subject of the recent decision in *Cutler* v. *Kennedy,* No. 77-0734 (D.D.C. July 16, 1979). In that case, the court held that "FDA may not lawfully maintain Category III in any form in which drugs with Category III conditions * * * are exempted from enforcement action." (*Cutler, supra.,* slip op. at 38). The agency is presently studying the effect of this decision on the OTC drug review procedures. Accordingly, although this document retains the concept of Category III in its original form, the agency's response to the court's decision may result in substantial changes in the regulatory treatment of Category III conditions.

In the **Federal Register,** of January 5, 1972 (37 FR 85), FDA announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. In the **Federal Register,** of May 11, 1972 (37 FR 9464), the agency published the final regulations providing for the OTC drug review under § 330.10

which were made effective immediately. Pursuant to these regulations, FDA issued in the **Federal Register**, of December 12, 1972 (37 FR 26456) a request for data and information on all active ingredients utilized in OTC topical analgesic, including antirheumatic, otic, burn, sunburn treatment and prevention, drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness, and labeling of those products: Thomas G. Kantor, M.D., chairman; John Adriani, M.D.; Col. William A. Akers, M.D.; Maxine Bennett, M.D.; Minerva S. Buerk, M.D.; Walter L. Dickison, Ph.D.; and Jerry Mark Shuck, M.D.

The Panel was charged to review submitted data information on OTC topical analgesics, including antirheumatic, otic, burn, and sunburn treatment and prevention active ingredients. For purposes of this review, the Panel grouped the active ingredients and labeling into four major pharmacologic groups—external analgesics, skin protectants, topical otics, and sunscreens.

The Panel presents its conclusions and recommendations for external analgesic active ingredients in this document. For discussion purposes, the external analgesic active ingredients have been further divided into four pharmacologic groups—topical anesthetics, topical antipruritics, topical counterirritants, and topical analgesics. The Panel's conclusions for topical otic active ingredients were published in the **Federal Register** of December 16, 1977 (42 FR 63556); the conclusions for sunscreen active ingredients were published in the **Federal Register** of August 25, 1978 (43 FR 38206); and its conclusions for skin protectants were published in the **Federal Register** of August 4, 1978 (43 FR 34628).

The Panel was first convened on March 6, 1973 in an organizational meeting. Working meetings were held on May 8 and 9, July 12 and 13, September 27 and 28, November 3 and 4, November 26 and 27, 1973; January 30 and 31, March 6 and 7, April 10 and 11, May 8 and 9, June 10 and 11, July 17 and 18, September 24 and 25, October 22 and 23, November 26 and 27, 1974; January 21 and 22, March 13 and 14, April 17 and 18, May 21 and 22, July 15 and 16, September 30 and October 1, November 12 and 13, 1975; March 4 and 5, May 19 and 20, June 22 and 23, September 27 and 28, November 18 and 19, 1976; February 23 and 24, May 25 and 26, August 22, 23, and 24, October 25, and December 13, 14, and 15, 1977; February 21, 22, and 23, April 19 and 20, and May 22 and 23, 1978.

The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration (address given above).

Seven nonvoting liaison representatives served on the Panel. Jacqueline Pendleton (at the initial meeting), Valerie Howard, (from May 8, 1973 to September 28, 1973), Lynn Berry (from November 3, 1973 to April 27, 1976), Kathleen A. Blackburn (from July 6, 1976 to August 24, 1977), and Emily Londos (from October 25, 1977) were nominated by an ad hoc group of consumer organizations and served as the consumer liaison. Joseph L. Kanig, Ph.D., nominated by the Proprietary Association, and Ben Marr Lanman, M.D., nominated by the Cosmetic, Toiletry, and Fragrance Association, until February 21, 1977, served as the industry liaisons.

The following FDA employees served: C. Carnot Evans, M.D., served as executive secretary; Lee Geismar served as panel administrator; Lee Quon, R.Ph., served as drug information analyst until July 1973, followed by Thomas H. Gingrich, R.Ph., until July 1975, followed by Timothy T. Clark, R.Ph., until July 1976, followed by Victor H. Lindmark, Pharm.D., until February 1978, followed by Thomas J. McGinnis, R.Ph.

The following individuals were given an opportunity to appear before the Panel, either at their own or at the Panel's request, to express their views on the issues before the Panel: Joseph P. Armellino, M.D.; Robert Blank, Ph.D.; Charles Bluestone, M.D.; Stuart Ericksen, Ph.D.; Carol Farhi, Esq.; Alexander A. Fisher, M.D.; Thomas Fitzpatrick, M.D., Ph. D.; J. M. Glassman, M.D.; Peter Hebborn, Ph.D.; George E. Heinze; Kenneth R. Johannes; Albert M. Kligman, M.D.; Howard Maibach, M.D.; Edward Marlowe, Ph.D.; Kenneth L. Milstead; John Parrish, M.D.; Madhue Pathak, M.D.; Leroy H. Possley; Robert Sayre, Ph.D.; Joseph P. Soyka, M.D.; Carrett Swenson, Esq.; Stephen M. Truitt, Esq.; and Frederick Urbach, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through May 23, 1978, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings on external analgesic drug products are set out in three categories:

Category I. Conditions under which OTC external analgesic drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC external analgesic drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of December 12, 1972 (37 FR 26456), the following firms made submissions related to the indicated products:

A. Submissions by Firms

Firms and Marketed Products

Abbott Laboratories, North Chicago, IL 60064: Butesin Picrate Ointment with Metaphen, Tronothane Hydrochloride Cream, Tronothane Hydrochloride Jelly.

Arnar-Stone Laboratories, Inc., Mount Prospect, IL 60056: Americaine Aerosol Spray, Americaine Ointment, Americaine Sunbalm, Americaine-12 Aerosol Spray, Americaine-12 Ointment.

B. F. Ascher and Co., Inc., Kansas City, MO 64030: Mobisyl Creme.

Astra Pharmaceutical Products, Inc. Worcester, MA 01606: Xylocaine Ointment.

Beecham Products, (formerly Calgon Consumer Products Co., Inc.), Rahway, NJ 07065: S. T. 37.

Berry and Withington Co., Cambridge, MA 02140: Analgesic Balm.

Block Drug Co., Inc., Jersey City, NJ 07302: Omega Oil.

Bowman Pharmaceuticals, Inc., Canton, OH 44702: Almophen Ointment, Analgex Ointment, Benz-Pic Ointment, Calamine Compound Paste, Caloxal Lotion, Liquid Analgesic Green, Liquid Analgesic White.

Brown Medicine Co., Knoxville, TN 37917: Brown's N&B Liniment.

Carbisulphoil Co., Dallas, TX 75204: Foille Liquid, Foille Ointment.

Ciba-Geigy Corp., Summit, NJ 07901: Nupercainal Cream, Nupercainal Ointment, Nupercainal Spray, Pyribenzamine Cream, Pyribenzamine Ointment, Vioform Hydrocortisone.

Otis Clapp and Sons, Inc., Cambridge, MA 02139: Obtundia Antiseptic Swab Pads, Obtundia Cream, Obtundia Calamine Cream, Obtundia First Aid Spray, Obtundia Surgical Dressing.

Combe, Inc., White Plains, NY 10604: Johnson's Soak 'N Massage, Lanacane Cream, Lanacane Spray.

Denver Chemical Manufacturing Co., Stamford, CT 06904: Antiphlogistine Poultice, Dencorub, Painaway.

The Dow Chemical Co., Zionsville, IN 46077: Dyclone Cream.

Eneglotaria Medicine Co., Inc., Santurce, PR 00907: Balmaflex, Linimento Daire.

Gebauer Chemical Co., Cleveland, OH 44104: Gebauer's Tannic Spray.
Geriatric Pharmaceutical Corp., Floral Park, NY 11001: Ger-O-Foam.
M. S. Glorius, Washington, D.C. 20021: Glorius Pain Relief.
C. F. Kirk Laboratories, Inc., New York, NY 10021: Exocaine Medicated Rub, Exocaine Plus.
Lilly Research Laboratories, Indianapolis, IN 46206: Surfacaine, Surfadil Cream, Surfadil Lotion.
Medical Supply Co., Rockford, IL 61101: MSCo Burn Compound, MSCo Burn Spray, Medicated Ointment, Telephone Ointment.
The Mentholatum Co., Inc., Buffalo, NY 14213: Mentholatum Deep Heating Lotion, Mentholatum Deep Heating Rub.
Meyer Brothers Drug Co., St. Louis, MO 63132: Bet-U-Lol.
Norwich Pharmacal Co., Norwich, NY 13815: Unguentine Aerosol with Benzocaine, Unguentine Ointment, Unguentine Plus, Unguentine Spray.
Noxell Corp., Baltimore, MD 21203: Noxzema Skin Cream.
Parke, Davis & Co., Detroit, MI 48232: Benadryl Cream, Caladryl Cream, Caladryl Lotion.
Pfizer Pharmaceuticals, New York, NY 10017: Ben Gay Greaseless/Stainless Ointment, Ben Gay Lotion, Ben Gay Ointment, Un-Burn.
Plough, Inc., Memphis, TN 38101: Dermasol Cream, Dermasol Foam, Dermasol Lotion, Dermasol Spray, Medicated Skin Cream, Medicated Skin Lotion, Medicated Skin Ointment, Musterole, Musterole Deep Strength Arthritis Pain Relief Rub, Musterole Extra Strength, Solarcaine Aerosol Spray, Solarcaine Cream, Solarcaine Foam, Solarcaine Lotion.
William P. Poythress & Co., Inc., Richmond, VA 23261: Panalgesic.
Quist Chemical Co., Niagara Falls, NY 14304: "A May's-on" Ointment.
Reed and Carnrick, Kenilworth, NJ 07033: Tarcortin.
Resinol Chemical Co., Baltimore, MD 21201: Resinol Medicated Cream, Resinol Medicated Ointment.
Rexall Drug Co., St. Louis, MO 63115: Thru, Intracel.
The R. Schattner Co., Washington, DC 20016: Chloraderm, Oraderm Lip Lotion.
Smith, Kline & French Laboratories, Philadelphia, PA 19101: Quotane Lotion, Quotane Ointment. C. G. Smith Products Co., Blytheville, AR 72315: Bob's Gypsy Rub Liniment #2.
Sperti Drug Products, Inc., Ft. Mitchell, KY 41017: Aspercreme.
E. R. Squibb & Sons, Inc., New Brunswick, NJ 08903: Counterpain Rub.
Sterling Drug, Inc., New York, NY 10016: Campho-Phenique Liquid, Campho-Phenique Powder, Medi-Quick Spray, Pontocaine Cream, Pontocaine Ointment.
Wade Chemical Corp., Shreveport, LA 71103: Jim Wade Deep Treet Liniment.
Warner-Lambert Research Institute, Morris Plains, NJ 07950: Sloan's Balm Analgesic, Sloan's Liniment.
Warren-Teed Pharmaceuticals Inc., Columbus, OH 43215: Myoflex Creme.
Whitehall Laboratories, Inc., New York, NY 10017: Anbesol, HEET, HEET GEL, HEET Spray, Infrarub, Outgro.
Yager Drug Co., Baltimore MD 21201: Yager's Liniment.
W. F. Young, Inc., Springfield, MA 01101: Absorbine Arthritic Pain Lotion, Absorbine Jr.

In addition, the following firms made related submissions:

Dermik Laboratories, Fort Washington, PA 19034: Hydrocortisone.
Monsanto Industrial Chemicals Co., St. Louis, MO 63166: Methyl Salicylate.
National Program for Dermatology, Washington, DC 20006: Hydrocortisone.
Plough, Inc., Memphis, TN 38101: Hydrocortisone Acetate.
E. R. Squibb and Sons, Inc., New Brunswick, NJ 08907: Lanolor, Lanolin with emulsifiers.
The Upjohn Co., Kalamazoo, MI 49001: Hydrocortisone.

Deferred from the Miscellaneous External Drug Products Review Panel:

Miles Laboratories, Inc., Elkhart, IN 46514: Cort-Dome Cream, Cort-Dome Lotion.

B. Labeled Ingredients Contained in Marketed Products Submitted to the Panel

As stated above, the Panel established four major groups, three of which (otics, sunscreens, and skin protectants) have been discussed in previous issues of the **Federal Register**. Since many currently marketed OTC drug products, which the Panel has classified in this document as external analgesics, also have other labeled ingredients which more appropriately may be classified as skin protectants or pharmaceutical necessities depending upon dosage and claims, the Panel has attempted in the following list to identify primarily those labeled ingredients in submitted products which are properly used and labeled as external analgesics. (See part III. paragraph B.1. below—Category I labeling.)

The Panel has identified the following labeled ingredients in marketed products:

Acetone
Acetone sodium bisulfite
Alcohol
Ammonium oleate
Aqua ammonia
Aspirin
Barbadoes tar
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
BHA
BHT
Boric acid
Butesin picrate (butamben picrate)
Calcium silicate
Camphor
Camphorated meta-cresol
Camphorated oil
Capsicum
Capsicum oleoresin
Carbolic acid
Carbomer 934
Carboset
Cellulose gum
Cetyl alcohol
Cetyl palmitate
Cetyl stearyl glycol
Chloral hydrate
Chlorbutanol
Chlorobutanol
Chloroform
Chlorothymol
Chloroxylenol
Citric acid
Clove oil
Coal tar extract
Color
Corn oil
Cyclomethycaine sulfate
Dibucaine
Diglycol stearate
Dimethisoquin hydrochloride
Dimethyl polysiloxane
Diphenhydramine hydrochloride
Dyclonine hydrochloride
Epsom salts
Essential oils and tinctures
Ethyl alcohol
Eucalyptol
Eucalyptus oil
Eugenol
Fragrances
Glycerin
Glycerine
Glycol monosalicylate
Glyceryl monostearate
Glyceryl stearate
Hexylresorcinol
Histamine dihydrochloride
Hydrocortisone
Hydrocortisone acetate
8-Hydroxyquinoline
Ichthammol
Iodine
Iodochlorhydroxyquin
Isopropyl alcohol
Isopropyl myristate
Isopropyl palmitate
Lanolin
Lanolin alcohol
Lanolin anhydrous
Lanolin derivatives
Lanolin oil
Lidocaine
Lidocaine hydrochloride
Lime water
Menthol
Merthiolate
Metaphen
Methapyrilene hydrochloride
Methylcellulose
Methyl nicotinate
Methylparaben
Methyl salicylate
Microcrystalline wax
Mineral oil
Mustard
Oil eucalyptus
Oil of cade
Oil of camphor
Oil of camphor sassafrassy
Oil of cloves

Oil of eucalyptus
Oil of lemon
Oil of peppermint
Oil of pine
Oil of turpentine
Oil of white camphor
Oil of wintergreen
Oil of pine tar
Oil turpentine
Oleoresin capsicum
Oleoresin of capsicum
Oleostearin
Oleth-3-phosphate
Oxyquinoline base
Oxyquinoline sulphate
Parabens
Parachlorometaxylenol
Paraffin
Parahydrecin™ (Norwich brand of anhydropara hydroxy mercuri meta cresol)
PEG 2 stearate
Phenol
Phenylmercuric acetate
Phenylmercuric nitrate
Picric acid
Poloxalkol
Polyoxyethylene sorbitan monostearate
Polyoxyl-40-stearate
Polysorbate 20
Pontocaine base (tetracaine)
Pontocaine hydrochloride (tetracaine hydrochloride)
Potassium oleate
Potassium stearate
Pramoxine hydrochloride
Propellant 46 (80 percent isobutane and 20 percent propane)
Propellant 12/114 (dichlorodifluoromethane/dichlorotetrafluoroethane)
Propylene glycol
Propylene glycol stearate
Propylparaben
Purified water
Quaternium 15
Resorcinol
Salicylamide
Salicylic acid
Sesame oil
Silica
Sodium bisulfite
Sodium borate
Sodium carbomer
Sodium citrate
Sodium lauryl sulfate
Sodium phenolate (phenolate sodium)
Sorbitan monostearate
Sorbitan oleate
Stearic acid
Stearyl alcohol
Synthetic methyl salicylate
Synthetic spermaceti
Talcum power
Thimerosal
Thyme oil
Thymol
4,2',4'-Trichloro-2-hydroxydiphenylether
Triclosan
Triethanolamine
Triethanolamine salicylate
Triethanolamine stearate
Tripelennamine hydrochloride
Tronothane hydrochloride (pramoxine hydrochloride)
Turpentine
Turpentine oil
Volatile oil of mustard
Volatile oils
Water
Wax
White wax
Wormwood oil
Zinc oxide
Zirconium oxide (as the carbonate)

C. Classification of Ingredients

1. *Active ingredients.*

Allyl isothiocyanate (mustard, volatile oil of mustard)
Ammonium water, stronger (aqua ammonia, ammonium oleate)
Aspirin
Benzethonium chloride
Benzocaine
Benzyl alcohol
Butamben picrate (butesin picrate)
Camphor (camphorated oil, oil of camphor, oil of white camphor)
Camphorated metacresol (camphorated metacresol)
Capsicum preparations: Capsaicin, Capsicum, and Capsicum oleoresin (oleoresin capsicum, oleoresin of capsicum)
Chloral hydrate
Chlorobutanol (chlorbutanol)
Cyclomethycaine sulfate
Dibucaine
Dibucaine hydrochloride
Dimethisoquin hydrochloride
Diphenhydramine hydrochloride
Dyclonine hydrochloride
Eucalyptus oil (oil eucalyptus, oil of eucalyptus, eucalyptol)
Eugenol (clove oil, oil of cloves)
Glycol salicylate (glycol monosalicylate)
Hexylresorcinol
Histamine dihydrochloride
Hydrocortisone preparations: Hydrocortisone, and Hydrocortisone acetate
Juniper tar (oil of cade)
Lidocaine
Lidocaine hydrochloride
Menthol
Methapyrilene hydrochloride
Methyl nicotinate
Methylsalicylate (oil of wintergreen, synthetic methyl salicylate)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Pramoxine hydrochloride (tronothane hydrochloride)
Resorcinol
Salicylamide
Tetracaine (pontocaine base)
Tetracaine hydrochloride (pontocaine hydrochloride)
Thymol
Triethanolamine salicylate
Tripelennamine hydrochloride
Turpentine oil (oil of turpentine, oil turpentine, turpentine)

2. *Inactive ingredients.* The Panel has classified the following as inactive ingredients or pharmaceutical necessities. The list is not intended to be exhaustive. In some cases, when used in concentrations at the level of or above the minimum effective dose, the ingredient(s) are also classified as active and included above in No. 1.

Acetone
Acetone sodium bisulfite
Alcohol
Aluminum acetate
Ammonium oleate (with less than 0.5 percent free ammonia)
Barbadoes tar
Benzalkonium chloride
BHA
BHT
Boric acid
Butyl stearate
Calcium silicate
Carbomer 934
Carboset
Cellulose gum
Cetyl alcohol
Cetyl palmitate
Cetyl stearyl glycol
Chlorothymol
Chloroxylenol
Citric acid
Color
Corn oil
Diglycol stearate
Dimethyl polysiloxane
Epsom salts (magnesium sulfate)
Essential oils and tinctures
Ethyl alcohol
Eucalyptus oil
Fragrances
Glycerin (glycerine)
Glyceryl monostearate
Glyceryl stearate
Isopropyl alcohol
Isopropyl myristate
Isopropyl palmitate
Lanolin
Lanolin alcohol
Lanolin anhydrous
Lanolin derivatives
Lanolin oil
Lime water
Menthol
Merthiolate (thimerosal)
Methylcellulose
Methylparaben
Methyl salicylate
Microcrystalline wax
Mineral oil
Nitromersol chloride (Metaphen)
Oil of lemon
Oil of peppermint
Oil of pine tar
Oleostearin
Oleth-3-phosphate
Parabens
Paraffin
Parahydrecin ™ (Norwich brand of anhydropara hydroxy mercuri meta cresol)
PEG 2 stearate
Phenol (carbolic acid)
Phenylmercuric acetate
Phenylmercuric nitrate
Picric acid
Pine oil
Poloxalkol
Polyoxyethylene sorbitan monolaurate
Polyoxyethylene sorbitan monostearate
Polyoxyl-40-stearate
Polysorbate 20
Potassium oleate
Potassium stearate
Propellant 46 (80 percent isobutane and 20 percent propane)
Propellant 12/114 (dichlorodifluoromethane/dichlorotetrafluoroethane)

Propylene glycol
Propylene glycol stearate
Propylparaben
Purified water
Quaternium 15
Salicylic acid
Sesame oil
Silica
Sodium bisulfite
Sodium borate
Sodium carbomer
Sodium citrate
Sodium lauryl sulfate
Sorbitan monostearate
Sorbitan oleate
Stearic acid
Stearyl alcohol
Synthetic spermaceti
Talcum powder
Thimerosal
Thyme oil
Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether)
Triethanolamine
Triethanolamine stearate
Volatile oils
Water
Wax
White wax
Wormwood oil
Zinc oxide
Zirconium oxide (as the carbonate)

3. *Ingredients deferred to other OTC advisory review panels or other experts.*

Benzethonium chloride
Benzoic acid
Chloroxylenol (parachlorometaxylenol)
Coal tar extract
8-Hydroxyquinoline
Ichthammol
Iodine
Iodochlorhydroxyquin
Magnesium sulfate (epsom salt)
Oxyquinoline base
Oxyquinoline sulfate (oxyquinoline sulphate)
Zirconium oxide (as the carbonate)

4. *Labeled ingredients no longer marketed.*

Chloroform
Oil of camphor sassafrass

D. Referenced OTC Volume Submissions

All OTC Volumes cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the **Federal Register** of December 12, 1972 (37 FR 26456). The volumes will be put on public display after January 3, 1980, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Introduction

The Panel was responsible for evaluating the safety and efficacy of individual active ingredients and combinations of active ingredients which are applied to the skin to relieve the symptoms of pain, itching, or irritation, and which as a group are designated "external analgesics." The Panel identified symptoms, in and under the skin, due to trauma, irritating chemicals, allergic reactions, toxins, physical agents such as infrared or ultraviolet radiation, or systemic disease.

External analgesics, like all other OTC medications, are intended to provide relief for symptoms that are self-limiting. They are not designed to be curative agents.

The Panel recognizes two distinct pharmacologic subgroups of active ingredients within the external analgesic group: ingredients that depress cutaneous sensory receptors and those that stimulate cutaneous sensory receptors. Because this subgroup classification is used throughout the document, it is important to state this distinction as early as possible. The pharmacologic subgroups are discussed at length in the section on pharmacological classification. (See part II. paragraph F. below—Pharmacology of External Analgesic Active Ingredients.)

External analgesic active ingredients which depress cutaneous sensory receptors for pain, itching, and burning act directly to diminish or obliterate these symptoms due to burns, cuts, abrasions, insect bites, and other cutaneous lesions. These ingredients may be further classified into three pharmacologic groups, i.e., topical analgesics, topical anesthetics, and topical antipruritics.

The other group of external analgesic active ingredients stimulates cutaneous sensory receptors to induce sensations such as burning, warmth, coolness, etc. These induced sensations serve as a distraction from the deep-seated pain in areas such as muscles, joints, and tendons which are distant from the skin surface where the ingredient is applied. In this manner, deep-seated pain is indirectly relieved. The ingredients which stimulate cutaneous sensory receptors can be further classified pharmacologically as topical counterirritants.

Some active ingredients, e.g., camphor, menthol, can depress cutaneous sensory receptors at low concentrations and stimulate cutaneous sensory receptors at high ones. These actions are discussed in individual ingredient statements specifying the dosages at which each action occurs. The Panel recognizes that two separate descriptions of an ingredient with a dual action, once as an ingredient which depresses cutaneous sensory receptors and elsewhere as an ingredient which stimulates cutaneous sensory receptors, would be confusing. Therefore, such ingredients are described under one ingredient statement.

The Panel has grouped all external analgesic ingredients together into this document, whether they depress or stimulate cutaneous sensory receptors, because all of these ingredients are applied to the skin to relieve painful sensations of one type or another.

Many products reviewed by the Panel were combinations of ingredients. They had labeling claims associated with the combination, not for each specific ingredient in the combination. Where this was the case, the Panel made a judgment and linked a specific claim with a specific ingredient.

B. Definitions

The following are definitions of terms used in this document:

1. *Addition.* The combined effect of two or more similarly acting therapeutic agents binding at the same receptor site. This is in contrast to "summation," which applies to agents binding at separate receptor sites. The effect of addition is greater than each would produce alone in the particular concentration used, e.g., benzocaine combined with tetracaine.

2. *Base (organic).* An organic base is a nitrogenous compound which is alkaline in an aqueous medium and is capable of forming salts with acids.

3. *Bioactive.* The moiety of a bioavailable substance or an active metabolite that exerts the intended therapeutic effect on a receptor site.

4. *Bioavailability.* The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.

5. *Burns.* The Panel recognizes the following types of burns:

a. *Thermal burns.* Injuries to the skin resulting from exposure to heat or infrared radiant energy.

b. *Sunburn.* An injury to the skin resulting from exposure to ultraviolet (UV) radiant energy.

c. *Chemical burns.* An injury to the skin resulting from exposure to certain chemicals.

6. *External analgesic.* A topically applied substance that may have a topical analgesic, anesthetic, antipruritic, or counterirritant effect as defined below.

7. *Haptene.* An incomplete antigen incapable of causing the production of antibodies but capable of neutralizing specific antibodies in vitro.

8. *Hydrophilic.* A substance with an affinity for water.

9. *In vitro.* A laboratory study on the physical, chemical, or therapeutic properties of an agent. Such a study is not performed on living animals or man. An in vitro study may be done in laboratory equipment with material obtained from a human or animal body.

10. *In vivo.* A study performed on living animals or man.

11. *Lipophilic.* A substance with an affinity for lipids.

12. *Organoleptic.* A property of a substance which makes an impression upon one or more of the organs of special sense, thereby affecting the flavor, odor, or appearance of a drug product.

13. *Partition.* The distribution of a therapeutic agent between two contiguous phases, i.e., a lipid phase and an aqueous phase, or between cells of a cutaneous surface and a medium in which a therapeutic agent is dissolved or dispersed.

14. *Partition coefficient.* The concentration ratio of distribution of any substance between two immiscible liquids. For example, if 26 grams (g) of a drug are dissolved in a unit volume of water and the solution is then shaken with an equal volume of olive oil, and 25 g of this drug pass into the oil phase and 1 g of the drug remains in the water phase, the partition coefficient for oil to water is 25.

15. *Skin conditions*—a. *Intact skin.* This term refers to a cutaneous surface in which the stratum corneum has not been disrupted and has not lost its integrity or continuity.

b. *Damaged skin.* A surface in which the stratum corneum barrier is disrupted.

(1) *Injured intact skin.* Skin or other cutaneous surfaces in which the stratum corneum remains intact but edema, inflammation, or other pathologic processes are present in the lower layers as a result of injury from physical or chemical agents and disease.

(2) *Abraded skin.* A cutaneous surface in which stratum corneum has lost its continuity as a result of trauma and permits access of drugs and other substances to the cells beneath.

(3) *Excoriated skin.* A cutaneous surface that has been disrupted by the trauma of scratching.

16. *Summation.* An effect of the combination of two or more similarly acting therapeutic agents binding at separate receptor sites. The effect results in a response that is greater than each agent produces alone in the particular concentration used, e.g., an antihistamine combined with a topical anesthetic.

17. *Topical analgesic.* An externally applied substance that relieves pain without necessarily abolishing other sensations, or one that causes partial blockade of subcutaneous terminal nerve endings so that a minimal stimulus evokes no painful response, but a greater stimulus does.

18. *Topical anesthetic.* An externally applied substance that completely blocks pain receptors, resulting in a sensation of numbness and abolition of responses to painful stimuli.

19. *Topical antipruritic.* An externally applied substance that relieves itching.

20. *Topical counterirritant.* An externally applied substance that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints, or viscera distal to the site of application.

C. The Skin and Skin Penetration

1. *General discussion.* The skin is an organ that protects man from his environment. Both the skin and its underlying structures often undergo pathologic changes that are annoying, uncomfortable, or even incapacitating. These pathologic changes may be manifestations of some systemic disease or local microbial infection in the skin, or they may be induced by trauma, physical agents, and exogenous or endogenous chemical agents. Some of these pathologic processes are self-limiting and disappear or heal spontaneously. Before they heal they are accompanied by annoying symptoms such as pain, burning, or itching. These symptoms are amenable to self-treatment. Other skin conditions, more serious and progressive in nature, are not amenable to self-treatment and should be treated by a physician (Ref. 1).

Since antiquity man has applied to or rubbed into his skin a variety of drugs to relieve symptoms of pain, burning, and itching. Today a considerable number of OTC preparations, which are promoted as providing relief from these symptoms, are available to the American public. To evaluate the safety and efficacy of such preparations, it is necessary to be familiar with certain aspects of the skin's anatomy and physiology and to have some understanding of the mode of action of these drugs and how they penetrate the epithelial and sub-epithelial barriers.

The Panel relied upon standard references and texts and on its own expertise for information on the anatomy and physiology of the skin (Refs. 1 and 2). The conclusions below were drawn from the information at hand.

Adult human skin refers to the skin of humans older than 6 months of age. Although it is possible that penetration of drugs through geriatric skin differs from drug penetration through skin of younger adults and may warrant special consideration, the Panel obtained no information which allowed it to come to a conclusion on this issue.

Skin of those under the age of 6 months may also have different absorptive characteristics. The Panel was concerned with possible differences in percutaneous absorption between infant skin and adult skin. Maibach, a recognized authority, addressed the Panel on the subject.

Maibach (Ref. 3), citing the results of several studies, stated that, depending on the compound being tested, infant skin is relatively similar to adult skin with respect to percutaneous absorption. He noted, however, that the skin of premature infants had a greater degree of drug absorption than either skin of term infants or the skin of adults. Propylene glycol, in an in vitro experiment, was applied to cadaverous skin from infants, premature infants, and adults. The drug penetration of the infant skin and the adult skin was similar, but the penetration through the premature infant skin was tenfold greater than through term infant skin.

A correlation was also made by Maibach between hexachlorophene myelinopathy and premature infant deaths. He described a study in which it was found that there were more deaths attributable to hexachlorophene in the premature infant than in the term infant.

In another study on percutaneous absorption in the newborn, a vasoconstrictor was applied to infant skin and the degree of blanching was observed. There was a definite correlation between the degree of blanching and the gestational age. The premature infant skin permitted greater penetration of the vasoconstrictor than the term infant skin.

To provide an added margin of safety, the ingredients reviewed below are not to be used for children under the age of 2 years except on the advice of a physician. Although the Panel has defined adult skin as skin that is older then 6 months of age, the added margin of safety between 6 months and 2 years of age, is considered important because of the sensitive nature of the problems of medicating infants.

By the age of 2, a child is walking, verbally communicating, and better able to express his or her symptoms and feelings to a parent who would apply a topical medicament. The infant under 2 years of age is more passive and less able to express and localize symptoms.

The effects of occlusion from a diaper, lying on a waterproof mattress, wet clothing, or from body folds touching each other can cause disease and enhance cutaneous penetration of medicaments. Occlusion of adult skin by impervious materials or wet cloth has been demonstrated to cause prickly heat (miliaria) within 48 hours, enable fungi to attack the skin within 72 hours, and permit a 100-fold rise in cutaneous bacteria in 6 hours. The penetration of hydrocortisone is enhanced 10- to 100-fold by occlusion. The Panel is concerned about the effects of a high local concentration of a drug on the integument itself under the occlusive conditions which exist in infants. Ingredients under occlusion may possibly be corrosive to the infant's skin. Biologic systems which metabolize and excrete drugs absorbed through the skin may not be fully developed in children less than 2 years of age.

The Panel concludes that its subsequent considerations of safety and efficacy of OTC drug products are suitable for humans 2 years old and older. Children under 2 should receive these drugs only under the advice and supervision of a physician.

While obvious differences are known to exist between male and female skin, the Panel believes that these differences are not likely to affect the safety or efficacy of the various drugs considered.

2. *Skin penetration.* Three important factors which affect penetration of the skin by drugs are physiological factors, physicochemical factors, and pathological factors.

a. *Physiological factors.* Among the physiological factors affecting the penetration of drugs through the intact skin are the arrangement of the layers of cells in the cutaneous barriers, differences in arrangement of the layers and the types of cells comprising them; differences in thickness or arrangement at various anatomic sites of the body; electrical charges present in the proteins and ions in various layers of the epithelial barriers; the water content of the skin; and the blood flow in a particular area of skin (Refs. 1 and 2). There are three possible portals of entry through the human skin—the epidermal barrier, the hair follicles, and the sweat glands.

For practical purposes, all absorption occurs through the epidermal barrier and hair follicles. The epidermal barrier consists of the stratum corneum which is a keratophospholipid complex that can be as much as 1,500 microns in thickness.

The penetration of drugs occurs more readily through damaged skin because the horny layers of the skin have been disrupted, and the drug readily passes through the undermost layers of the stratum corneum into the dermis. Stripping the epidermis by the application of adhesive tapes, vigorous scrubbing, or brushing alters the barrier and allows drugs that ordinarily do not penetrate to pass into the skin and produce analgesia (Refs. 4 and 5). Active ingredients thus come into direct contact with the receptors for various sensations but particularly those forming the network of nerve endings that sense pain, burning, and itch. Abraded, excoriated, or burned skin permits ready access to these nerve endings and the analgesic effect may be more intense than it is when only superficial layers of the epidermis are removed. In some cases, particularly when the skin is abraded or cut, and the receptors are exposed completely, total blockade results and the subject may experience the sensation of numbness or anesthesia. Other receptors, such as those that carry sensations of touch, pressure, cold, or warmth, may also be blocked. This may not be the case on intact skin (Refs. 4 and 6).

Studies in cadaver skin suggest that absorption is directly related to skin thickness, and that it is greater in areas where large hair follicles are present.

Absorption of medications applied to areas in close apposition to other skin areas, such as the axilla (arm pit) and the groin (crotch), may be different. Less may be absorbed and the remainder may be more irritating than in other locations because of the presence of moisture and constant friction. Specialized glands found in the ear canal produce a waxy, protective secretion that may limit the contact of medication to the skin surface. Mucous membranes in close apposition to the skin, such as in the mouth, the inner aspects of the labia, and the borders of the eyelids absorb medications more readily than the adjacent or junctional skin (Refs. 2 and 7).

Human skin appears to be unique and its characteristics regarding drug absorption are not mimicked exactly by any other species.

b. *Physicochemical factors.* (1) Drug absorption is facilitated by hydrating the skin which is capable of absorbing a considerable amount of water. Complete occlusion by physical means can increase absorption of a drug.

(2) The variations in environmental temperature greatly affect absorption.

(3) As a rule, increasing the concentration of ingredients in a preparation leads to increased absorption by the skin. However, in almost every instance, a plateau effect eventually occurs, which may be followed by a reduced rate of absorption at high concentrations due to an effect on the skin itself or to a high concentration of the drug in the skin, which may inhibit further absorption.

(4) The Panel accepts the concept that lipid-soluble substances diffuse through the lipid portion of the skin barrier and water-soluble substances diffuse through the hydrated component of the proteins found within this barrier (Ref. 8). The partition coefficient of the drug and its vehicle in relation to the skin may be rate limiting. Substances soluble in both water and lipids penetrate the skin barrier more readily than those that are predominately hydrophilic or lipophilic (Refs. 1, 7, and 8).

(5) Generally, smaller molecules penetrate more rapidly than larger molecules. Substances up to the size of 1,000 daltons (molecular weight 1,000) are usually absorbed readily while larger ones are absorbed with greater difficulty. Polar groups are readily absorbed. Molecular configuration unquestionably affects absorption. However, the mechanisms involved are not well understood (Ref. 8).

(6) Vehicles are important in determining the absorption characteristics of the drugs and will be considered below. A drug should not bind with any component of its vehicle in such a manner that its partition with respect to the skin barrier favors retention in the vehicle (Refs. 8 and 9).

Although the original charge to the Panel was to review only active ingredients for safety and effectiveness, the Panel believes that the vehicle in which the ingredient or combination of ingredients is incorporated may influence the effectiveness of the ingredient or ingredients involved and must be considered. Known effects of inactive ingredients, therefore, are considered where pertinent in the discussions of the individual ingredient groups to follow.

The Panel stresses that in most cases continued contact of a film of the active ingredient is essential for efficacy. The medium in which an active ingredient is incorporated must provide not only the necessary solubility and stability, but must also maintain contact of the active ingredient with the lesion of the skin. The medium must not retard the passage of the drug into the skin or into lesions, thereby decreasing its bioavailability (Refs. 8, 9, and 10).

A drug's rate of release from its vehicle and consequently its ability to penetrate the skin barrier depend on the rate of diffusion of the drug within the vehicle. The vehicle may also affect the hydration of the stratum corneum. In general, vehicles which increase or

maintain hydration promote drug absorption, although there are exceptions (Refs. 5, 6, and 9).

Some solvents, such as dimethylsulfoxide and demethylformamide, when used as vehicles, may accelerate absorption of substances through the skin barrier. These solvents are still under investigation for possible use in man. Other compounds may decrease penetration.

Surface active agents (surfactants) may alter surface tension and increase absorption of polar compounds by the water within the skin.

Most vehicles consist of emulsions, i.e., suspensions of droplets of one liquid in another in which it is insoluble. Once an emulsion has separated into its components it is difficult to reconstitute. Large dispersed particles in an emulsion can separate and rise to the surface and cause creaming. A creamed emulsion may generally be reemulsified by shaking.

Emulsions may require stabilization which can be accomplished by the use of surfactants or soaps. Some vehicles discussed by this Panel contain anionic surfactants. These may be incompatible with cationic surfactants. Frequently emulsions support growth of molds and preservatives need to be added (Ref. 11).

Semisolid dermatologic vehicles are classified as ointments, pastes, or creams. In addition to emulsions, semisolid vehicles may be oleaginous vehicles consisting of hydrocarbons, fatty acids, or esters of fatty acids. Fatty acids and their esters may become rancid. Pastes or cerates are less fluid and stiffer than ointments. Absorption bases are composed of ingredients that are hydrophilic and absorb water. Newer formulations may incorporate Carbowaxes ™ and glycols of high molecular weight, approximately 1,500 daltons, which are solid and resemble petrolatum in consistency (Refs. 11 and 12).

Vanishing creams consist of oil-in-water emulsions that generally contain large percentages of water (75 percent or greater) plus stearic acid, stearyl alcohol, and a humectant such as propylene glycol. When applied to the skin with moderate friction, the emulsion breaks, the water is lost by evaporation, and the remaining film of stearic acid or stearyl alcohol is invisible. Thus the cream seems to vanish.

Some ingredients may alter the effectiveness of an active ingredient by shifting the pH of the medium in which the active ingredient is incorporated, thereby changing its ionization and lipophilic qualities. An active ingredient that is effective in the form of a free base may be less effective or ineffective as a salt (Ref. 12).

The concentration of ingredients in a film making contact with the skim is an important factor in assuring effectiveness. A partition or division of the ingredient occurs between the medium in which the ingredient is incorporated and the skin. This partition may vary for skin in different areas of the body (Refs. 4 and 11). Some drugs that are obviously effective when used in areas of the body such as mucous membranes may not be effective on the skin because they are formulated in such a manner that insufficient quantities are delivered to the skin. When a medium retains the ingredient and the partition coefficient is high (25 to 1), for example, 25 for the medium and 1 for the skin, the effectiveness may be reduced considerably so that the preparation is not effective. When a poorly water-soluble ingredient, for example 20 percent benzocaine, is dissolved in a medium such as propylene glycol, a bioactive amount is made available to the skin because the propylene glycol acts as a depot to saturate the water in the skin with the drug. A saturated aqueous solution does not ordinarily provide a bioactive amount. If tetracaine base or a base of a similar type of local anesthetic is dissolved in alcohol and applied as a lotion to the skin, the alcohol evaporates and the drug remains on the skin in powder from and is eneffective (Ref. 4). A vehicle that contains the drug and remains on the skin as a film and readily releases the active ingredient is necessary to formulate an effective final product. An ideal dermatological vehicle should be stable, neutral, nongreasy, nondegreasing, nonirritating, nondehydrating, nondrying, washable, odorless, and stainless. It should act efficiently on all kinds of human skin, should hold at least 50 percent water, and should be easily compounded with known chemicals (Refs. 1 and 11).

Vehicles in common use represent a compromise of advantages against disadvantages, many of which have been noted previously. It is difficult to predict with any degree of accuracy the influence of a vehicle fromulation on the percutaneous absorption of an active ingredient without actual testing of the complete drug. Some authorities believe that medicinals are absorbed more readily from animal or vegetable oils than from petrolatum bases.

Vehicles for topical delivery of active ingredients are complex mixtures of substances designed to impart a certain characteristic to the finished product. Although classified as inactive or inert ingredients, many vehicles interact physically and chemically with the outer layer of human skin (the stratum corneum). The substantivity, penetration, and resistance of the active ingredients to sweating, washing, and other factors often depend upon the vehicle.

The Panel strongly recommends that all inactive ingredients, including those in the vehicle, be listed on the labeling, preferably with a statement of quantity. The consumer or his or her physician may find it necessary to know the identity of all the ingredients in a product for a variety of reasons, including possible adverse patient responses (Refs. 1 and 11).

Therapeutic claims cannot be based on pharmacologic characteristics of inactive ingredients or vehicles. Since these substances are intended for topical application where cosmetic ellegance and cosmetic acceptance are considerations for the consumer, a description of the vehicle may be included in the labeling, e.g., nongreasy, nonstaining, oily, greaseless, velvety, emollient, moisturizer, nonsticky.

c. *Pathological factors.* Skin abnormalities may increase or decrease absorption of substances through the skin. Disease conditions, such as psoriasis and lichen simplex chronicus, decrease absorption through the skin because of the formation of thick plaques. Callous formations also interfere with the absorption of drugs through the skin. On the other hand, conditions such as eczema which cause thinning of the skin or oozing enhance the penetration of drugs through the skin.

References

(1) Criep, L. H., "Dermatologic Allergy," W. B. Saunders Co., Philadelphia, pp. 3–20, 1967.

(2) Andrews, G. C., "Diseases of the Skin," 4th Ed., W. B. Saunders Co., New York, pp. 66, 137, 163, 186, 1955.

(3) Summary Minutes of the OTC Panel on Topical Analgesic Drug Products, 27th Meeting, November 18, 1976.

(4) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics Through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

(5) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(6) Wolff, H. G. and S. Wolf, "Pain," Charles C. Thomas Publishing Co., Springfield, IL, pp. 3–10, 1958.

(7) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(8) Idson, B., "Percutaneous Absorption," *Journal of Pharmaceutical Sciences, 64:901-924, 1975.*

(9) Steiner, M., V. Gstirner, and R. Elsner, "Percutaneous Absorption of Salicylic Acid from Modern Ointment Bases," *Arzneimittel Forschung,* 14:281-286, 1964.

(10) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1523-1529, 1975.

(11) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 900-902, 1977.

(12) Davidson, C. and H. G. Mandel, "Non-narcotic Analgesics and Antipyretics: 1. Salicylates," *in* "Drill's Pharmacology in Medicine," Edited by DiPalma, J. R., McGraw-Hill Book Co., New York, p. 383, 1971.

D. Physiology of Pain

Pain is difficult to define. It is a multidimensional experience which involves both a discriminative capacity and an interpretation of a stimulus in terms of present and past experience (Ref. 1).

Receptors are present in the skin for the perception of pain, itching, cold, warmth, touch, and pressure (Ref. 2). The receptors for pain, cold, warmth, touch, and pressure are discussed in this section. A separate section of this document is devoted to the physiology of itching.

Topical analgesics, anesthetics, antipruritics, and counterirritants act at the site of application of a drug after they penetrate the skin and come into contact with receptors. These receptors are connected to terminal fibers of networks of nerves that are present in the various layers of the skin. Each perceives its own type of sensation.

Receptors are classified as follows: 1. *Receptors for pain.* These consist of bare nerve endings that receive the stimuli incited by pain directly and transmit them to larger nerve trunks to the central receptors in the brain. The nerve fibers carrying the sensation are mostly of the small unmyelinated C type (Ref. 1). Some delta A myelinated fibers may also play a role. Although pain fibers are not uniformly distributed over the body surface, they are estimated to average over 4,000 per square inch of skin. The activity of these receptors is obtunded partially or completely by topical analgesics, anesthetics, and antipruritics. They appear to be affected more easily and readily than the receptors for other sensations listed below, probably because they are small and unmyelinated and thereby easily penetrated by drugs (Ref. 2).

2. *Receptors for cold.* The end bulbs of Krause are oval sense organs in the skin that perceive the sensation of cold. These nerve endings may be blocked simultaneously with the pain receptors by analgesics, anesthetics, or antipruritics. Whether or not they are blocked depends upon the concentration that reaches them and the degree of penetration. They may be stimulated by some ingredients, such as menthol or camphor, and produce a sensation of coolness that masks the sensation of pain. Some counterirritants may act by stimulating these receptors.

3. *Receptors for warmth.* The end organs of Ruffini are cylindrical end organs in the skin that perceive the sensation of warmth. They may also be partially or completely blocked simultaneously by the analgesics, anesthetics, or antipruritics, depending upon the concentration and the duration of contact. They may also be stimulated by counterirritants, thereby exerting a topical analgesic effect.

4. *Receptors for pressure.* Pacinian corpuscles are cylindrical end organs in the skin perceiving the sensation of deep pressure. Analgesics and anesthetics in concentrations exceeding those needed to block pain receptors may block these receptors.

5. *Receptors for touch.* Meissner's corpuscles are end organs in the skin perceiving the sensation of touch. They may also be partially or completely blocked by analgesics, anesthetics, or antipruritics (Ref. 2).

While cutaneous pain is easily localized, deep pain arising below the skin is poorly localized, dull in quality, and spreads or radiates in a distinct pattern. The ability to localize pain is not inborn; it is learned. Deep pain is frequently referred, i.e. felt at locations remote from its source (Refs. 3 and 4).

Referred pain syndromes are numerous. Myocardial (heart) pain is referred to the arm or the jaw, diaphramatic pain to the shoulders, hip pain to the knee, etc. Some pain reference patterns are readily explained as overflows to contiguous spinal cord segments, but this is not always the case (Ref. 4).

Pain originating in bones, joints, and tendons ordinarily induces muscle hypertonus (spasm) and associated pain in supportive skeletal muscles. Much of the pain of degenerative joint disease and rheumatoid disease may arise from tight regional musculature rather than from direct impingement upon a sensory nerve. Such induced hypertonus and chronic muscle injury, with pain, is a part of the involuntary defensive mechanism whereby the human organism attempts reflexively to immobilize a painful joint by increasing the tone of the muscle pairs which serve the skeletal area involved (Ref. 5).

Pain threshold varies little among persons, but the psychological response to pain varies greatly among individuals and in the same individual under different circumstances and in differer settings. Time, place, situation, social factors, cultural, and family response patterns, and particularly an individual's interpretation of the meaning of the stimulus, determine whether the experience is regarded as painful (Refs. 1, 3, and 4).

Anxiety is an aspect of pain. There i probably no pain which does not have an anxiety component.

The placebo effect is important not only in OTC self-medication but in all aspects of the healing arts. Frank . consideration and acceptance of the psychosomatic contribution of specific OTC products is both desirable and appropriate. Response of an individual pain perception to a placebo effect is independent of the cause or mechanisr of the pain, more likely if pain is intens not peculiar to neurotic individuals, an not predictable (Refs. 1 and 6).

References

(1) Kabler, J. F., "Neural Mechanisms of Pain," Independent Study Program, University of Wisconsin Medical School, pp 6-14, September 1975.

(2) Best, C. H. and J. H. Taylor, "The Physiological Basis of Medical Practice," 7t Ed., The Williams and Wilkins Co., Baltimore, pp. 1139-1147, 1961.

(3) Kolodny, A. L. and P. McLoughlin, "Comprehensive Approach to the Theory of Pain," Charles C. Thomas Publishing Co., Springfield, IL, pp. 27-33, 1966.

(4) Wolff, H. G. and J. C Hardy, "On the Nature of Pain," *Physiology Review,* 27:167-199, 1947.

(5) Kabler, J. F. "Muscle Pain," Independer Study Program, University of Wisconsin Medical School, pp. 15-28, April 1973.

(6) Beecher, H. K., "Powerful Placebo," *Journal of the American Medical Association,* 159:1602, 1953.

E. Physiology of Itching

Itching is one of the most common an annoying skin symptoms for which user of OTC external analgesics seek relief. How the stimuli are evoked, how the impulses giving rise to the sensation are conducted, and how the sensation is perceived have been the subject of considerable study and speculation. There appears to be almost complete agreement among physiologists that the anatomic pathways subserving pain and itch are identical and that itching results when cutaneous pain fibers are weakly stimulated. In other words, the difference between stimuli causing pain and itch is one of intensity. Those causing itch are subminimal. Subjectively, weak pain is indistinguishable from itching. Objectively, the motor responses to pain differ from those evoked by itching. When pain is felt, there is a tendency to

withdraw from the pain. When itching is felt, there is a desire to scratch.

From the studies of various investigators (Ref. 1), it appears that impulses which subserve the itch sensation are carried by both the small, nonmyelinated Class C fibers and the large and more rapidly conductina myelinated fibers. the sensation of itch has two subjectively distinguishable components, one pricking and the other burning. The pricking sensation is mediated via the myelinated fibers; the burning sensation is mediated by the nonmyelinated fibers. It has been shown that intractable itching can be eliminated by sectioning of the spinothalamic tracts in the cord. The ability to appreciate the itch sensation may depend on some central mechanism for selective interpretation, however, other investigators have suggested that the sensation of itch results from impulses traveling in circuits in the internuncial neurons in the spinal cord, with a subsequent pattern discharge up along the spinothalamic tracts. It has been noted that itching in the skin can be abolished by stimulation of the skin, by pinprick, at a distance of 30 cm or more from the itch stimulus but apparently in the same dermatome. Following the sensations of pinprick, there is a lag of several minutes before the itch is felt again. Moreover, itch cannot be produced in an area of experimentally induced hyperalgesia. Either pain or no sensation is felt (Ref. 1).

Shelley and Arthur (Ref. 2) showed that itching sensation is limited to itch points in the skin. Between these points there are silent areas which do not respond to stimuli that induce itching. It was further shown histologically that itch points are endowed by rich subepidermal aggregates of fine nerve fibers which are absent in the silent areas. Recently, it has also been suggested that the gate theory is involved in the transmission of impulses of the sensation of itch (Ref. 3). In the studies supporting this concept, no intraepidermal nerve filaments and no encapsulated or organized nerve units were observed at the itch sites. Itching can be induced by chemical agents such as cowhage or itch powder. Shelley and Arthur (Ref. 4) showed that the active pruritogenic principle in cowhage was a proteolytic enzyme. They also found that certain plant and animal endopeptidases which were active at pH 7 produced pruritus. As a result of these studies, it was postulated that proteinases are chemomediators of pruritus and these are released in tissues as a result of trauma. The sources of these chemomediators include the epidermal cathepsin, capillary plasmin infiltrates, and fungal proteases. Histamine likewise has been incriminated in causing itching. These findings have been confirmed by others. Monash and Woessner (Ref. 5) treated proteolytic enzymes with heat and reported that heat destroyed proteolytic but not pruritogenic properties. The enzyme concentrations and their materials were considerably higher than those used by Shelley who felt that the pruritus in these studies was probably the result of nonspecific formed protein rather than proteinase action. Although over the years much has been written concerning mechanisms that cause itch, the subject is far from being fully understood (Ref. 3).

Itching may be local in the skin of a particular area of the body or it may be generalized, depending on its etiology, which is multivaried. Localized itching may be due to stimuli arising in a particular area of the skin. Itching may also be generalized due to some systemic cause, such as jaundice, uremia, an allergic state, or other causes. the treatment of localized areas of itching is amenable to topically applied OTC products. Itching due to systemic causes usually requires the attention of a physician and systemic drug treatments.

External analgesics that relieve itch are called antipruritics. Since the sensation of itch is mediated via pain fibers, local anesthetics and analgesics that block conduction along the axonal membranes, such as the nitrogenous drugs of the "caine" type and of the alcohol type, all have antipruritic activity when used in adequate doses in proper formulation. Drugs that decrease inflammation and remove the stimuli that cause pruritus, such as the steroids, are also used to relieve itching. Since itching can be due to chemomediators, certain drugs that act competitively or combine with chemical agents released by trauma and other factors, such as antihistamines, relieve itching.

References

(1) Wolff, H. G. and S. Wolf, "Pain," *in* "American Lecture Series in Physiology," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 42–43, 1958.

(2) Shelley, W. B. and R. P. Arthur, "The Neurohistology and Neurophysiology of the Itch Sensation in Man," *Archives of Dermatology*, 76:296–323, 1957.

(3) Herndon, J. H., "Itching: The Pathophysiology of Pruritus," *International Journal of Dermatology*, 14:465–484, 1975.

(4) Shelley, W. B. and R. P. Arthur, "Studies on Cowhage (Mucuna Pruriens) and Its Pruritogenic Proteinase, Mucunan," *Archives of Dermatology*, 72:399–406, 1955.

(5) Monash, S. and J. M. Woessner, "Pruritus and Proteolytic Enzymes," *Archives of Dermatology*, 78:214–217, 1958.

F. Pharmacology of External Analgesic Active Ingredients

1. *Topical analgesics.* Topical analgesics are externally applied substances that relieve pain without causing numbness. Some are topical anesthetics that in subanesthetic doses partially depress cutaneous pain receptors and thereby produce analgesia. They may act by penetrating the cutaneous barriers and blocking receptors for the perception of pain. Such ingredients penetrate the nerve endings and cause a temporary reversible charge in the nerve membrane, preventing the development of the electrical current at a given point in a nerve fiber that transmits the impulses along a nerve (Ref. 1).

Some ingredients may, in one concentration, stimulate cutaneous sensory receptors and when they act in this manner are referred to as counterirritants. In lower doses, they depress cutaneous pain receptors and exert an analgesic effect. Menthol is an example of such an ingredient. In concentrations exceeding 1.25 percent in certain vehicles, it causes counteriritation and excites cutaneous senory receptors. In concentrations less than 1.0 percent, it depresses cutaneous pain receptors and acts as a topical analgesic in a manner similar to phenol and other alcohols. Certain esters of salicylic acid which are used as counterirritants, such as methyl salicylate, are claimed to be analgesic when applied topically to the skin at less than the counterirritating dose, due to percutaneous absorption and the release of salicylic acid (Refs. 2 and 3). This action is discussed in more detail below.

Some drugs exert analgesic effects by eliminating a painful stimulus. These agents reduce swelling of the tissues or they neutralize noxious chemical substances that are released by trauma, an infection, or another process (Ref. 4). The three groups of drugs thought to act in this manner are salts and esters of salicylic acid and pharmacologically allied compounds; the adrenocorticosteroid hormones; and the antihistamines.

Inflammation is a pathologic process that occurs in the blood vessels and adjacent tissues (Refs. 5 and 6). It is caused by a physical, chemical, or biologic agent, or a combination of one or more of these agents and is a manifestation of an organism's defense reaction. Inflammation is characterized by heat, redness, swelling, and

tenderness of the affected tissues. The amount of blood in the vessels near the inflamed area increases, and a transudation of fluid and white blood cells from the capillaries into the intercellular spaces occurs. This causes swelling which in turn causes stretching of the tissues, or pressure, and excitation of pain and other receptors (Ref. 7).

Certain drugs overcome or reduce these pathologic changes in tissues, thereby removing the stimulus that causes the pain or itching. Salicylates exert their analgesic effects both centrally and peripherally. Some pharmacologically related drugs, such as phenacetin, produce analygesia systemically but lack anti-inflammatory peripheral effects. The peripheral anti-inflammatory effect of the salicylates appears to be exerted upon tissues derived from endoderm and mesoderm and not on those derived from ectoderm (Ref. 10). Since skin is derived from ectoderm, it is reasonable to assume that pain in the skin is not relieved by salicylates. Salicylates may elicit an analgesic anti-inflammatory response by interference with prostaglandin biosynthesis at the cellular level, which may explain their peripheral effect (Refs. 7 and 9). Percutaneous absorption of salicylates has been demonstrated by detecting salicylates in blood and urine. The Panel regards the effects of percutaneously absorbed salicylates as systemic and considers their action to be the same as internal analgesics. The Panel finds no conclusive evidence that they exert any action in the skin (Ref. 9). There is no evidence that salicylates interfere with nerve impluse conduction and block transmission of painful impluses from the pain receptors in the skin. Evidence that salicylates exert anti-inflammatory action on the skin and relieve pain in the skin itself as do the topical anesthetics, antipruritics, and analgesics is lacking (Ref. 9). Thus, claims that salicylates applied to the skin relieve pain, such as that due to subburn and cuts, is without merit. Relief of deep-seated pain is the result of a systemic effect which may follow percutaneous absorption if the interstitial fluid drug concentration obtained is sufficiently high (Ref. 2).

The adrenocortical hormone, cortisone, and synthetic analogues have the capacity to prevent or suppress the development or cause the regression of the local heat, redness, swelling, and tenderness accompanying inflammation (Ref. 5). These drugs belong to a group called adrenocorticosteroids, also called corticosteroids or steroids. They inhibit the development of the early phenomena of inflammatory processes such as the formation of edema, capillary dilatation, the migration of phagocytes into an inflamed area, and possibly inhibit the release of noxious chemical agents or toxins. One theory is that these anti-inflammatory agents in pharmacologic concentrations stabilize the membranes of lysosomes in the cells and prevent the disruption that occurs from influences such as hypoxia, bacterial and chemical toxins, antigen-antibody complexes, and physical agents such as heat and light. Enzymes in the lysosomes such as proteases, peptides, or other chemicals cause inflammation if they leak outside the cells. All that is known for certain about the mode of action of adrenocorticosteroids is that they obviously inhibit the inflammatory responses of mechanical, chemical, or immunological origin (Ref. 11).

Adrenocorticosteroids relieve pain by reducing inflammation and thereby removing the pain stimulus. Steroids have been especially useful in the symptomatic relief of cutaneous lesions of allergic origin. But the use of anti-inflammatory agents, such as steroid hormones or salicylates, is strictly palliative. After their use, the underlying disease process may remain and the symptoms may recur. For this reason the Panel emphasizes that preparations containing steroids for topical use should be used for short-term therapy only, and should not be used if symptoms recur unless so advised by a physician. The development of corticosteroid preparations suitable for topical administration has revolutionized the therapy of more common varieties of skin disease. Steroids have replaced many of the traditional remedies used in the treatment of various eczematous lesions, such as atopic dermatitis, contact dermatitis, etc., and have been of great value in the treatment of such disorders accompanied by pruritus (Ref. 5).

Drugs that act antagonistically to histamines are called antihistamines (Refs. 8, 12, and 13). The antihistamines are nitrogen-containing compounds. They resemble the nitrogen-containing local anesthetics in some respects, depending upon their structural configuration. They possess one or more amine groups, are bases, and form salts with acids. Some are derived from ethylenediamine, such as tripelennamine, and others from ethanolamine, such as diphendydramine. The salts are highly ionized, highly water soluble, and hydrophilic. The bases are poorly ionized, poorly water soluble, lipophilic, and their absorption through the intact skin is similar to the "caine" type of topical anesthetics. The structure of antihistamines, in some respects, resembles the general configuration characteristic of the "caine" drugs. However, there is sufficient modification so that they do not cause systemic effects similar to the "caine" drugs. When they pass into the circulation, the actions of antihistamines overlap the actions of other drugs (anticholinergic, antinauseant, etc.) (Ref. 1).

2. *Topical anesthetics.* Topical anesthetics are externally applied substances that completely block pain receptors, resulting in a sensation of numbness and abolition of responses to painful stimuli (Refs. 14 and 15). These anesthetics may also block receptors of cold, warmth, pressure, and touch, resulting in the subjective sensation of numbness (Ref. 1).

There are two types of topical anesthetics, the nitrogen-containing amino type and the hydroxy or alcohol type (Ref. 16). The nitrogen-containing topical anesthetics consist of diverse chemical types described below. A certain particular chemical configuration appears in the majority of the most potent and serviceable topical anesthetics. This configuration is composed of a hydrocarbon nucleus (benzene ring) and a two-carbon chain bearing the nitrogen atom in the form of a tertiary amine. The hydrocarbon nucleus forms an acid in some compounds; this acid is combined with an alcohol which carries the amino group to form an ester. The ester types of topical anesthetics are the most widely used in OTC products; examples are benzocaine, butamben, and tetracaine.

A second kind used in OTC products, known as the amides, consists of a benzene ring linked to the two-carbon chain by an amide group. The two-carbon chain carries the tertiary amino group. Lidocaine and dibucaine are amides used in OTC preparations (Ref. 16).

The benzene ring, the aromatic portion, is called the lipophilic pole since it is oriented toward fatty materials in cells and toward the nerve membranes which contain large quantities of fatty materials. The water-soluble or hydrophilic amino pole is opposite the aromatic pole, separated by the carbon chain. It becomes oriented into the water phase of a medium or a cell or cell membrane.

The generic names of most topical anesthetics end in the suffix "caine." The "caine" type of compounds are categorized as the water-soluble (tetracaine, lidocaine) and as the relatively insoluble derivatives

(benzocaine, butamben). The so-called insoluble anesthetics are poorly soluble but not totally insoluble, otherwise they would not be effective (Refs. 1 and 16). However, the amount dissolved in water is low. Soluble compounds are readily absorbed from the damaged skin. When applied to large areas, for example 50 percent of the body surface of abraded, excoriated, or otherwise damaged skin, they may be rapidly absorbed in quantities great enough to cause the development of toxic plasma levels that result in life-threatening or even fatal reactions. Toxic reactions are characterized by initial stimulation of the nervous system, manifested by convulsions, followed by depression, paralysis, and cessation of respiration. In addition, these drugs also depress the cardiovascular system, affecting the heart, reducing its output, and relaxing the blood vesseles so that a decrease in blood pressure occurs.

The systemic reactions are referred to as the central nervous system type or the cardiovascular type. Both types may occur simultaneously, but generally the central nervous system type of reaction is the most prominent and occurs first (Ref. 17). When applied to small lesions, the quantities absorbed from the intact or damaged skin are not sufficient to cause reactions. As long as these drugs are in the area of the nerve endings and pass slowly from the tissue fluids into the blood stream, the amount circulating in the blood is insignificant and causes no systemic reaction (Ref. 17). These types of systemic reactions have occurred so rarely following the wide use of these ingredients in OTC products when applied on the skin that the Panel does not consider them to be a serious hazard.

Some nitrogen-containing topical anesthetics have structures that are modifications of the classical type of "caine" drugs with an aromatic nucleus attached to the remainder of the molecule by a ketone, ether, or other type of linkage instead of the ester and amide type (Ref. 16). The names in this group of topical anesthetics usually bear the suffix "ine" instead of "caine." Pramoxine and dyclonine are nitrogen-containing compounds that are examples of non-"caine" type drugs. Their molecules are modified sufficiently so that they are effective topically, but if absorbed do not produce the systemic response of the severity cahracteristic of the "caines." If injected, they are irritating or not effective. They do not cause convulsions, but may cause cardiac depression. These drugs are not as effective as the "caine" type drugs. Some antihistamines have structures that are modifications of the "caine" type of topical anesthetics. They possess, in addition to the antihistamine effect, a topical anesthetic effect (Refs. 1 and 16). Their names also bear the suffix "ine." These are described elsewhere in this document. (See part II. paragraph F.1. above—Topical Analgesics.

The second type of topical anesthetic mentioned above, the alcohol type, is nonnitrogenous. The alcohol type drugs, such as phenol, benzyhl alcohol, etc., do not cause central nervous system or cardivascular effects characteristic of the "caine" type drugs. Systemic effects, if they occur at all, vary with the individual alcohol type drug.

The water-insoluble esters such as benzocaine and butamben are not absorbed in sufficient quantities to produce plasm levels that cause systemic reactions and, therefore, are relatively safe. Convulsions and cardiac depression do not occur from the use of this type of compound. These have been used in oral preparations without any serious toxic effects. They are effective on the mucous membranes as well as on the skin, poor water solubility notwithstanding, because they are soluble in glycols and other similar types of water soluble bases. When solutions prepared with these solvents are applied to a surface, sufficient quantities are delivered to pain receptors to produce analgesia and anesthesia. Benzocaine is one of the safest and most widely used of the OTC topical anesthetics (Refs. 18 and 19).

Salts of bases of topical anesthetics, antihistamines, and alkaloids are usually very water soluble and highly ionized. They are not highly lipophilic and do not readily penetrate lipid barriers of cell membranes. Such salts do not penetrate the intact skin, or, if they penetrate, they do so slowly and in insignificant quantities.When the salt is neutralized with an acid, the free base is released. The free base is poorly soluble in water, but soluble in lipids and readily penetrates the intact skin. These salts are described in the individual ingredient statements. Where claims are made that a preparation of a salt is effective on the intact skin, the Panel recommends testing for effectiveness as described elsewhere in this document. (See part III. paragraph C.5.d. below—Methods of studying salts of bases.)

3. *Topical antipruritics.* Sensations of pain and itch are carried by the same type receptors and nerve filaments; the intesity of the stimulus varies (Ref. 26). (See part II. paragraph E. above—Physiology of Itching.)

Some antihistamines relieve the discomfort of itching due to histamine release in allergic states when applied to the skin, not only by competing with histamine, at the H_1 receptors (one of 2 broad classes of histamine receptors), but also by their topical anesthetic effect. The antihistamines are more effective orally than topically as antipruritics, particularly when itching is generalized. They may be effective in localized areas if the itching is due to histamine release. Since not all itching is due to histamine release, the antihistamines may not always produce the effect claimed in the labeling (Ref. 13). The Panel finds no evidence to support claims that imply that antihistamines stop itching caused by the release of serotonin, various kinins, and other chemical mediators. The antihistamines, formulated as salts, do not readily penetrate the intact skin. The base, however, does penetrate. When the stratum corneum has been disrupted, penetration by the salt readily occurs and the claimed effect is obtained if the discomfort is due to histamine. Thus, the absorption of antihistamines through the skin is similar to the absorption of the "caine" type of drugs and associated compounds.

Other drugs that relieve itching are the steriods and local anesthetics. These have been mentioned above. Evidence that salicylates exert a topical antipruritic effect is lacking.

4. *Topical counterirritants.* Topical counterirritants are included among the external analgesics because they are applied to the intact skin for the relief of pain. They differ from the anesthetics, analgesics, and antipruritic agents, however, in that the pain relief they produce results from stimulation—rather than depression—of cutaneous sensory receptors and occurs in structures of the body other than the skin areas to which they are applied as, for example, in joints, muscles, tendons, and certain viscera (Ref. 21). The use of these products dates from antiquity. Counterirritants act by producing a transient, reversible, and mild inflamation or irritation of the skin (Refs. 21 and 22).

Drugs used to induce counterirritation do not belong to any particular chemcial class as do the topical anesthetics, the antihistamines, and antipruritic agents. The chemical structures are quite diverse. Some are phenolic in nature; others are aromatic oils derived by distillation from various types of wood. Others are obtained from vegetable sources, such as capsicum and mustard. A number may exert a placebo effect through pleasant aromatic odors or a sensation of warmth or coolness which they produce on the skin. Some are not

single entity products but rather mixtures of closely allied compounds or isomers.

Although some neurophysiologists have at times directed their attention to counterirritants, precisely how these drugs act to relieve pain is still far from understood. It is well recognized that pain may be referred to a segment of normal skin subserved by the same spinal nerve that subserves a diseased or injured muscle, bone, joint, or viscus. Presumably, from evidence at hand, counterirritants stimulate the receptors in the skin and produce a milder pain, such as itching or burning, or some other less unpleasant sensation, such as warmth or coolness, which obscures a more severe pain in a structure other than the skin to which they are applied. Thus, counterirritation may be considered to be reverse of referred pain which is felt in an area of the skin when a disease process or injury exists in a structure and the same nerves serve them both (Ref. 21). The practice of voluntarily producing a counter milder pain to relieve a more intense pain is instinctive. Crossland (Ref. 23) introduces the subject of counterirritation as follows: "In order to make intense pain more tolerable the sufferer will bite his lips or clench his fists, digging the nails into the palm of the hand. The voluntary pain this produces reduces the preception of the other."

The gate theory of Melzack and Wall (Ref. 24) has considerable appeal among those interested in studies of pain mechanisms. In brief, this theory holds that exciting certain nerve fibers through sensations of warmth, mild burning, and mildly painful sensations causes a neurophysiological structure in the spinal cord, known as the gate, to close partially so that sensations from other nerve fibers are not transmitted in their entirety. Whether this mechanism is involved in pain relief induced by counterirritants has not been fully established. If the gate is involved, it may not be the only neurophysiological mechanism involved. Other mechanisms that have not been studied may also play a role.

The Panel mentions this concept of the gate mechanism to emphasize the fact that pain relief is accomplished by the substitution of one sensation by another. The phenomenon whereby the threshold of one type of sensory stimulus is modified by the concomitant application of another stimulus is called extinction. Extinction is believed to be a manifestation of the brain's inability to receive and interpret all of the impulses that are transmitted to it coupled with the subject's efforts to concentrate upon the inflow of voluntarily induced pain stimuli or stimuli from application of agents that produce counterirritation. There is no doubt that the action of counterirritants has a psychic component as well as a drug-induced therapeutic component. Whatever relief is obtained from the use of counterirritants is temporary, transient, and symptomatic. The Panel finds no convincing evidence that counterirritants exert any curative effect.

Besides using topical medicaments, counterirritation may be accomplished by physical means, such as using heat lamps and pads, infrared rays, diathermy, microwaves, ultrasound, hot packs, etc. Most medical practitioners use counterirritation as adjuncts to other forms of therapy and rely principally on physcial methods for counterirritation. The number who prescribes drugs for this purpose is very limited indeed. Marketing experience of counterirritants for OTC use is indicative of widespread popularity, but the Panel does not regard this popularity as proof of effectiveness of these products.

Counterirritants exert their effects in various ways. Some counterirritants induce a sensation of warmth. The intensity of the response of the skin depends not only upon the chemical nature of the irritant employed but also upon its concentration, the solvent in which it is dissolved, and the period of contact. At low concentrations, some counterirritants act as rubefacients, i.e., they cause redness but not inflammation of the skin. At higher concentrations, they may induce varying degrees of inflammation and have a vesicant or blistering action. The less the inflammatory response, the safer the drug (Ref. 21). When inflammation is induced, plasma escapes from the capillaries, which in turn causes blisters. Some counterirritants, such as menthol or camphor, at low concentration induce a sensation of coolness rather than warmth and produce analgesics. (See part II. paragraph F.1. Above—Topical analgesics.)

The Panel does not accept claims that counterirritants relieve pain by penetrating the skin and passing into muscles, joints, and other structures.

Some counterirritants with rubefacient activity produce an increase in the temperature and local blood flow at and near the site of application (Ref. 25). Likewise, dillation of the blood vessels at and near the site of application can be demonstrated following topical administration of rubefacients (Ref. 26). Evidence that there is an increase in conduction velocity in peripheral nerves following the percutaneous application of counterirritants to the intact skin may be of considerable significance (Ref. 27) since this observation is consistent with, and lends support to, the gate theory of Melzack and Wall (Ref. 24) mentioned above.

The theoretical mechanisms of pain relief by medication-induced counterirritation are described in numerous authoritative publications (Refs. 23, 26 and 28 through 31).

The types of vehicles used to formulate the finished product containing counterirritants are important.

Percutaneous absorption of counterirritant drugs is generally undersirable. Therefore, the finished product should consist of ingredients and vehicles that keep penetration through the skin at or as near a zero level as possible.

Self-medication with OTC counterirritant preparations may result in harm if directions are not exactly followed. Some individuals overreact to the irritant properties of counterirritants and develop rashes and blisters. The Panel therefore strongly urges that the following warning appear in the labeling of these products: "Discontinue use if condition worsens or if symptoms persist for more than 7 days and consult a physician." The Panel also recommends that the following additional warnings appear on the labeling to alert the consumer to avoid improper use of the OTC counterirritants: "Do not apply to wounds or damaged skin" and "Do not bandage."

5. *Summary.* Most external analgesic ingredients provide temporary symptomatic relief and are not curative. The steroids and possibly the antihistamines may ameliorate the disease process. Relief of symptoms beyond the time the medicament exerts its analgesic, antipruritic, anesthetic, or counteriritant effect sometimes occurs from the use of agents that directly or indirectly decrese or overcome muscle spasm, reduce edema, or alter the degree of blood flow in an affected area of the skin. A sequence sometimes facetiously referred to as the "vicious cycle" may be disrupted by one application of a topical analgesic, anesthetic, or antipruritic agent. Exactly how this comes about is not known. Possibly nociceptors in an injured area that send impulses centrally along special paincarrying fibers, called delta A and C fibers, are blocked when subjected to continuous stimulation by noxious stimuli. The threshold for stimulation is lowered and very light

stimuli induce pain. Such pain may be referred to adjacent spinal segments. Blocking the receptor may cause a restoration to its normal threshold level when the block is terminated. Whatever the mechanism may be, the vicious cycle phenomenon is occasionally observed in the management of pain problems (Ref. 32).

G. Safety of External Analgescis

All analgesic ingredients are capable of producing adverse reactions either topically or systemically. The systemic reactions are described in part II. F. above or in the ingredient statements when a reaction is peculiar to an ingredient. The reactions include side effects due to overdosing, intolerance, and idiosyncracy.

Some ingredients can irritate both intact and damaged skin when applied topically (Refs. 33 and 34). A rash may appear after one or more applications of such an ingredient when no rash existed prior to its use. This type of response occurs when the ingredient has a direct irritating effect on the cells and is termed primary irritant contact dermatitis. No immunological phenomena are involved. This type of response may be detected by using patch and other tests. (See part III. paragraph C, below—Data Required for Evaluation.) Irritation of the skin is deliberately induced by counterirritation with certain select ingredients whose action can be controlled. However, certain patients may overreact and a greater degree of irritation than is ordinarily expected may result after one or two applications.

In addition to irritation, counterirritants may also produce sensitization, in which case immunological phenomena are involved. The manifestations of sensitization may be topical or systemic. Topical sensitization in certain individuals may result from prolonged or repeated contact of an ingredient with the skin (Refs. 8, 33, and 35). Under these circumstances an ingredient may serve as a contact allergen by acting as a haptene and becoming bound to proteins of the skin. Stimulation of the T cell division of the lymphoid system occurs, and lymphoid cells that are sensitive to the contact allergen or the haptene accumulate in the skin. Contact with the ingredient at a later date provokes a cell-mediated sensitivity kind of reaction, termed allergic contact dermatitis. This is characterized by inflammation, pruritus, burning, erythematous macules, papules, exudation, crusting, etc. at the site of application. Immune globulins are not involved in this type of response (Refs. 36 and 37). Topical sensitization may, at times, be difficult to distinguish from direct topical irritation. The resulting contact sensitivity in a particular individual manifests immunological specificity for the particular ingredient (haptene). Patch testing may be used to detect this type of sensitization. (See part III. paragraph C. below—Data Required for Evaluation.) Coombs and Gell (Ref. 36) have classified immune responses into four distinct types. They designate this type of immune response (i.e., topical sensitization) as Type IV (Cytotoxic), in which the allergen or the haptene interacts with the sensitized lymphocytes.

A haptene can be inhaled, injected, or taken orally; it can come in contact with a mucous membrane, or pass through damaged skin and bind with proteins in blood and other tissue fluids to produce a systemic type of sensitization. This type of sensitization is due to immune globulin E (IgE) of the blood protein fraction. Coombs and Gell (Ref. 36) designate this as the Type I response. It occurs in the allergic individual and is associated with a hereditary tendency toward sensitization which is called atopy. Such individuals are sometimes referred to as atopic. Drugs combine with proteins and act as allergens that cause systemic type of sensitization stimulating the production of circulating antibodies (immune bodies).

Antibodies are found in the globulin fraction of blood proteins. Ordinarily immune bodies are protective and neutralize an antigen or a haptene, forming an antibody-antigen complex on contact, and no allergic reactions occur. In susceptible individuals, the antibody-antigen complex acts in an adverse (pathologic) manner and sensitizes certain target cells. IgE antibodies, which are increased in atopic individuals, have a cytophilic affinity for the membranes of mast cells, blood neutrophils, and basophils in susceptible individuals (Ref. 36). These antibody-sensitized cells rupture on subsequent contact with an allergen-haptene (drug) antibody complex and release vasoactive substances that dilate or constrict blood vessels. Other mediators of inflammation are also released. At least one or more exposures and an incubation period of a week are necessary for immune bodies and sensitization to develop.

The B cell division of the lymphoid system is involved in the systemic type of immune response (Ref. 36). The presence of antibodies that sensitize cells is necessary for sensitivity reactions to occur. This type of sensitization may be manifested by anaphylaxis, extrinsic asthma (systemic), rhinitis (systemic), subcutaneous edema, laryngeal and pharyngeal edema (systemic), urticaria, or atopic dermatitis (Ref. 37).

The initiation of antibody formation requires that antigen binds on the surface of a lymphocyte. The binding sites on a lymphocyte are called antigenic receptors. Only select sites on an antigen molecule are involved in binding at the antibody receptor site. These sites on an antigenic molecule are called antigenic determinants and account for a particular antigen having a specificity for a particular antibody.

Only restricted portions of antigenic molecules are involved in actual binding with antibody-combining sites (Refs. 36 and 38). Haptenes are low molecular weight, well-defined chemical substances. They are not immunogenic, but they do react with antihaptene antibodies. Haptenes conjugate with aminoacid or aminoacid complexes on proteins and induce the formation of antihaptene antibodies. The conjugated haptene behaves as a complete antigenic determinant of the protein with which it is conjugated. A protein carrier can therefore have its own set of native antigenic determinants, plus the new determinant of the conjugated haptene. Antigenic determinants have an overall three-dimensional shape. The antigenic determinants and the antibody sites with which they combine possess a structural complement similar to a lock and key arrangement. A haptene can react with an antibody without being bound to a protein if it fits into the receptor. Drugs that are in the same chemical family and are accommodated by the same receptors of an antibody may cross-react. However, even a slight modification of chemical structure between two closely, chemically allied drugs may negate this type of reaction if the haptene does not fit into the antibody receptor. Aminobenzoic acid, for example, is closely allied chemically to its ester, ethyl aminobenzoic acid (benzocaine). Yet it does not necessarily follow that both of these compounds will be accommodated by the same antibody receptor and cross-react even if they bind with the same complex of a protein (Refs. 36 and 38). In some cases the fit of the haptene is poor, resulting in a slight degree of cross-reactivity and a mild allergic response. Once a patient is sensitized to a haptene and carries the antihaptene antibody in the blood and tissues, contact with a haptene causes an adverse response without binding to a protein. The Panel finds that the incidence of cross-reactivity and cross-sensitization of analgesic ingredients is

low and does not consider this to be a problem (Ref. 36).

Human IgE antibodies will also fix to the plasma membranes of mast cells in the skin and cause sensitivity reactions when the appropriate antigen (or haptene) circulates in blood or comes into contact with these cells following percutaneous absorption. The response is cutaneous and can be local or generalized. The systemic type of sensitization differs from the topical, which is due to a contact allergen, causing a cell-mediated type of reaction rather than an adverse response to an antigen-antibody complex acting on sensitized target cells (Ref. 36).

The anaphylactic type of reaction to an analgesic agent is the most serious. This reaction may occur suddenly, with little or no warning, and may be fatal. A trace of the ingredient penetrating the damaged skin of a sensitized person may precipitate the sudden release of mediators, such as massive quantities of histamine, serotonin, slow release substance (SRS–A), or various kinins, etc. These mediators acting on the blood vessels cause them to dilate and may cause syncope, shock, and death in a matter of minutes. Marketing experience of topical analygesic ingredients indicates that the frequency of anaphylaxis from topical application on the skin has been rare.

In the absence of immune bodies, the drug itself may act directly on mast and other cells and cause histamine or other mediator release. This type of reaction is called anaphylactoid and resembles anaphylaxis, but the causative mechanism is different (Ref. 36). Fortunately, this type of reaction also is rare. Testing for sensitivity in this type of patient may be dangerous because the quantity used for testing may be fatal in susceptible individuals. An anaphylactic or anaphylactoid reaction may occur in the first time a drug is applied to the skin. The anaphylactic and anaphylactoid types of reactions may be delayed, but the manifestations, when fully developed, are similar to the instantaneous type.

Other manifestations of systemic sensitization that may occur are relatively benign and disappear with proper treatment or discontinuing use of the drug. Among these manifestations are rhinitis, asthmatic attack, urticaria (hives), and atopic dermatitis. Generally, histamine is the most common offender in causing these responses, but other mediators may also be responsible (Ref. 36).

All drugs can act as haptenes and cause sensitization. Antihistamines, desite their being used systemically for treating allergies, can act as haptenes and be sensitizers when applied topically. The "caine" types of local anesthetics and modifications of the "caine" type cause sensitization to a greater extent than the alcohol type of ingredients, although the alcohols also may produce irritation and sensitization. The salicylic acid derivatives can also act as haptenes and be sensitizers when applied topically.

The Panel believes that the long-term use and wide marketing experience of the majority of the ingredients it reviewed justifies their continued use and that hazards due to sensitization are minimal. However, subjects who are allergic to foods, inhalants, and other substances are high risks and are more apt to become sensitized to drugs (Ref. 34). Also, reactions to topically applied analgesic medications occur with greater frequency than from systemic use of these ingredients. Therefore, the labeling of external analgesic ingredients must indicate prompt discontinuation of a drug when sensitization occurs after one or more applications, or after repeated use, and advise the individual to consult a physician. The Panel recommends the following warning in the labeling: "Discontinue use if condition worsens or if symptoms persist for more than 7 days and consult a physician."

References

(1) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology*, 17:223–242, 1977.

(2) Beautner, R., B. Calesnick, E. Powell, and L. Bortin, "On the Absorption and Excretion of Methylsalicylate Administered by Inunction," *Journal of Laboratory and Clinical Medicine*, 28:1655–1662, 1943.

(3) Steiner, M., V. Gstirner, and R. Elsner, "Percutaneous Absorption of Salicylic Acid from Modern Ointment Bases," *Arzneimittel Forschung*, 14:281–286, 1964.

(4) Modell, W., H. Schild, and A. Wilson, "Applied Pharmacology," W. B. Saunders Co., Philadelphia, pp. 394–396, 1976.

(5) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 1487–1488, 1975.

(6) "Dorland's Illustrated Medical Dictionary," 25th Ed., W. B. Saunders Co., Philadelphia, pp. 779–780, 1974.

(7) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 92, 161–164, 977–979, 1973.

(8) Modell, W., H. Schild, and A. Wilson, "Applied Pharmacology," W. B. Saunders Co., Philadelphia, pp. 41–44, 145–154, 1976.

(9) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 325–358, 1975.

(10) Lim, R. S., F. Guzman, D. W. Rodgers, K. Goto, C. Braun, G. D. Dickerson, and R. J. Engle, "Site of Action of Narcotic and Non-narcotic Analgesics Determined by Blocking Bradykinin-Evoked Visceral Pain," *Archives Internationales de Pharmacodynamice et de Therapie*, 152:25–58, 1964.

(11) Osol, A. and R. Pratt, " The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 29–36, 1973.

(12) Goodman, L. S. and A. Gilman, " The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 603–612, 1975.

(13) Osol, A. and R. Pratt, " The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 146–149, 1973.

(14) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 263, 1977.

(15) deJong, R. H., " Physiology and Pharmacology of Local Anesthesia," 1st Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 3–7, 1970.

(16) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d. Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(17) Adriani, J., " Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner*, 25:82–86, 1962.

(18) Adriani, J. and D. Campbell, " Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association*, 162:527–530, 1956.

(19) Adriani, J. and R. Zepernick, " Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association*, 188:711–716, 1964.

(20) Wolff, H. G. and S. Wolf, "Pain," Charles C. Thomas Publishing Co., Springfield, IL, pp. 3–10, 1958.

(21) Sollman, T., " A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, pp. 118–121, 1948.

(22) Goodman, L. S. and A. Gilman, " The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 951–952, 1975.

(23) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 560–563, 1970.

(24) Melzack, R. and P. D. Wall, "Pain Mechanisms: A New Theory," *Science*, 150:971–979, 1965.

(25) Lange, K. and D. Weiner, " The Effect of Certain Hyperkinemics of the Blood Flow Through the Skin," *Journal of Investigative Dermatology*, 12:263–269, 1949.

(26) Fulton, G. P., E. M. Farlier, and A. P. Moreci, " The Mechanism of Action of Rubefacients," *The Journal of Investigative Dermatology*, 33:317–325, 1959.

(27) Post, B. S., S. F. Benton, and J. G. Benton, "The Effect of Percutaneous Medication on Motor Nerve Conduction Velocity," *Archives of Physical Medicine and Rehabilitation*, 45:460–465, 1964.

(28) Krantz, J. C., Jr. and C. J. Carr, "Pharmacological Principles of Medical Practice," 7th Ed., The Williams and Wilkins Co., Baltimore, pp. 765–767, 1968.

(29) Ferguson, F.C., "Drug Therapy," Lea and Febiger, Philadelphia, pp. 312–324, 1962.

(30) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 719–720, 1975.

(31) Cushny, A. R., "A Textbook of Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, pp. 197–203, 1918.

(32) Kitihata, L. M., R. G., McAlister, and A. Taub, "Identification of Trigeminal Nociceptors," *International Symposium of Pain, Advances in Neurology,* 4:83–89, 1974.

(33) Criep, L. H., "Dermatologic Allergy," W. B. Saunders Co., Philadelphia, pp. 3–20, 1967.

(34) North American Contact Dermatitis Group, "Epidemiology of Contact Dermatitis in North America 1972," *Archives of Dermatology,* 108:537–540, 1973.

(35) Gordon, B. L., "Essentials of Immunology," 2d Ed., F. A. Davis and Co., Philadelphia, pp. 110–112, 126, 1974.

(36) Coombs, R. R. A. and P. G. H. Gell, "Classification of Allergic Prescriptions Responsible for Clinical Hypersensitivity and Disease," *in* "Clinical Aspects of Immunology," 3d Ed., Blackwell Scientific Publications, London, pp. 761–781, 1975.

(37) Lane, C. G. and R. Luikart, "Dermatitis from Local Anesthetics with a Review of One Hundred and Seven Cases from the Literature," *Journal of the American Medical Association,* 146:717–720, 1951.

(38) Harper, H. A., V. W. Rodwell, and P. A. Mayes, "Review of Physiological Chemistry," 16th Ed., Lange Medical Publications, Los Altos, CA, pp. 602–608, 1977.

H. Effectiveness of External Analgesic Products

1. *Formulation effects.* Reliable objective methods for determining the efficacy of externally applied ingredients are not available. Therefore, the conclusions of the Panel are drawn from data from both controlled and uncontrolled subjective studies. Many of these studies were performed by private agenices and investigators under contract to industry and are unpublished. They were provided in submissions fo FDA by industry. Studies of independent investigators whose reports have been published in the medical literature have also been used to make evaluations. The Panel has also given consideration to reports of long-term, widespread satisfactory clinical use and marketing experience in evaluation of ingredients.

The majority of externally applied preparations submitted to the Panel for review consist of combinations of active ingredients used with pharmaceutical necessities, which are listed as inactive ingredients. The remainder are single entity active ingredients used with pharmaceutical necessities. The Panel recognizes that to be effective, the final product must be formulated properly and conform to accepted pharmaceutical manufacturing standards. Otherwise the active ingredient or ingredients are not bioavailable, or, if they are bioavailable, they are present in less than the effectve minimum dose or not in the forms that exert the intended therapeutic effects.

Important factors which the Panel considered in making its evaluations include the concentration of the active ingredients in the medium in which they are incorporated; viscosity and volatility of the medium; method of maintaining contact of the active ingredient with the skin for the necessary length of time to assure penetration and maximal therapeutic effect; acidity or alkalinity of the medium; and stability of the final product. Another important consideration to which the Panel gave weight was whether the inert ingredients or active ingredients in a preparation interact and nullify the action of the principal active ingredients (Ref. 1). The designation of pharmaceutical necessity as inactive or inert does not necessarily indicate that such an ingredient is chemically or pharmacologically inactive. An ingredient in a formulation containing more than one active ingredient could diminish the efficacy of another ingredient by retarding its absoprtion into the skin or the cutaneous lesion to which it is applied, by altering the alkalinity or acidity of the medium and thereby changing the degree of ionization and its ability to penetrate epithelial barriers, or by binding it in such a manner that it is not released or absorbed (Refs. 1, 2, and 3). On the other hand, when two analgesics, anesthetics, antipruritics, or counterirritants are combined, addition or summation may occur (Ref. 4).

The medium in which an active ingredient is incorporated must provide not only the necessary solubility and stability, but also must maintain contact of the active ingredient with the lesion of the skin. Such a medium must not retard the passage of the drug into the skin or into the lesions, thereby decreasing the bioavailability of the drug (Refs. 1, 2, 5, 6, and 7).

The Panel recognizes that drugs that are effective on the mucous membranes may not be effective on the intact skin. In some cases, concentrations that are safe and effective and recommended for use on the mucous membranes may be inadequate on the intact skin, and the concentration must be increased to be effective (Refs. 1, and 2), but then they may not be safe. However, it is the concensus of the Panel that no safety or efficacy testing is necessay for Category I ingredients or Category I combinations except as required for compliance with current good manufacturing practices.

References

(1) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics Through Epithelial Barriers," *Anesthesia and Analgesia,* 50: 834–841, 1971.

(2) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12: 913–919, 1971.

(3) Steiner, M., V. Gstirner, and R. Elsner, "Percutaneous Absorption of Salicylic Acid from Modern Ointment Bases," *Arzneimittel Forschung, 14: 281–286, 1964.*

(4) Adriani, J., et al, "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

(5) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(6) Hardy, J. D., C. B. Potelunas, and M. D. Meixner, "Pain Threshold Measurements on Human Skin Following Application of Topical Analgesics," *Journal of Investigational Dermatology,* 16:369–377, 1951.

(7) OTC Volume 060132.

2. *Techniques of application and their relation to effectiveness.* All of the ingredients reviewed by the Panel are applied to the skin surface to achieve their therapeutic effects. Some ingredients must be applied as a continuous film and must maintain their integrity in order to be effective. Other ingredients must be rubbed gently into the skin without inflicting trauma to facilitate absorption (Ref. 1). Vigorous rubbing or massage is recommended with still other ingredients for effectiveness.

Because the Panel recognizes it is possible that the beneficial effects of some topical medications, particularly when treating musculoskeletal disorders, may be due entirely to the rubbing and massage rather than to the pharmacologic action of the applied preparation, particular attention was given to this technique. Massage causes an increase in flow of blood and lymph in the skin and underlying structures (Refs. 2 and 3).

Massage has been used as a form of therapy for centuries. The concept of rubbing an irritated part is ancient. The term is believed to be Hebrew in origin, being derived from the word "mashesh" in the original text of the Old Testament. The first use of the word in its present connotation appears in a French textbook of medicine published in 1779.

If one examines the older reports of physicians who were strong advocates of massage, one finds little scientific data on massage techniques that prove or disprove their effectiveness. Despite this, the art was and still is widely practiced.

In the 18th century massage therapy fell into disrepute. It was resurrected during the middle and late 19th century by physicians, both in Europe and the United States, who agreed that massage was a useful tool and conducted physiologic and biochemical studies to obtain data that might explain its effectiveness. Investigators examined the effect of massage on absorption of fluid from joints and the abdominal cavity, and measured changes in venous blood flow and skin temperatures induced by massage. They found increases in all these parameters. Some reported that massage had a diuretic effect. In 1890 a study conducted in Italy indicated that massage delayed the onset of fatigue inactively contracting muscles. In addition, histological studies were performed on experimental animals demonstrating that changes were induced in muscle by massage. The healing of fractures in dogs allegedly was influenced in a salutary manner by massage. At the turn of the century, physicians and therapists began to use mechanical devices, such as vibrators, instead of manual techniques to perform massage.

Two divergent schools of thought evolved concerning massage. One was the so-called reflex massage concept, also known as connective tissue massage. This concept was based upon the premise that tenderness was present at the actual site of a disease process, and that rubbing the tender areas utilizing a variety of graded but increasingly complicated techniques of massage produced beneficial effects. The opposing view championed that concept of deep massage, which was based upon the premise that there is no direct relationship between the area of tenderness and the site of actual tissue damage. The tenderness is a referred superficial response mediated by the actual injured part. The injured part may be deep or distal to the site of the actually perceived tenderness.

In present-day therapeutics, massage is used primarily in physical and rehabilitation medicine. Orthopedists also give considerable attention to the technique. The application and rubbing in of medicaments is deemphasized or completely ignored in many descriptions of massage techniques. The consensus is that the massage itself causes the beneficial response. Studies comparing massage with other modalities are virtually nonexistent because it is difficult to prepare protocols for conducting controlled objective clinical studies on the therapeutic effectiveness of massage techniques. Many clinicians have found that massage is therapeutically beneficial in select situations and utilize it extensively.

The Panel has considered the various modes of application of topical products and has used the general term "apply" in the sections on proposed dosage to denote all methods of application that are commensurate with the active ingredients, the dosage form, and the type of vehicle employed, e.g., emulsion, vanishing cream, lotion, aerosol, ointment. Some examples of modifications of "apply" include: "apply freely," "flow on freely," "rub," "rub in well," "rub in gently," "rub on well," "rub in until it vanishes," "massage," "massage in," "spray," or "spray on."

I. Labeling of External Analgesic Products

The Panel concurs with the general labeling requirements adopted by FDA for OTC drug products. The labeling should indicate the concentration, the manner of usage, and the frequency of applications. In addition, the labeling should emphasize the necessary steps that must be taken to insure that the proper amount is present on the affected area to produce the claimed therapeutic effect.

After reviewing the submitted labeling for external analgesic products, the Panel recommends the following additional labeling requirements:

1. *Ingredients.* The Panel concludes that these products should contain only active ingredients plus inactive ingredients that are necessary for product formulation or that provide a distinctive product characteristic which is beneficial to the consumer. The Panel recommends that all such drug products identify in the labeling both active and inactive ingredients. The concentrations of the active ingredients present in the preparation should be listed and the officially recognized established name of the ingredients should be used.

2. *Indications.* The indications for use should be simply and clearly stated. For external analgesic pharmacologic groups, i.e., analgesic, anesthetic, and antipruritic drugs, the Panel concludes that the indication statement should be "for the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations." For counterirritant drugs the statement should be "for the temporary relief of minor aches and pains of muscles and joints, such as simple backache, lumbago, arthritis, neuralgia, strains, bruises, and sprains." (See part III. paragraph B.1. below—Category I Labeling.) The Panel used the terms in the above list of indications because it believes these terms would be understood by the general population. These are not necessarily terms which physicians would use in specific diagnoses. These general statements encompass the many slightly different claims, with the same connotation, in the labeling of currently marketed OTC external analgesic preparations.

For hydrocortisone and hydrocortisone acetate, the Panel concludes that the indication statement should be "for the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

3. *Warnings.* The Panel recommends that the labeling of OTC products containing the ingredients reviewed in this document includes the following warnings:

a. "For external use only." This warning is reasonable and prudent.

b. "Avoid contact with the eyes." The eye is not protected by an epidermal keratinized layer as is the skin. Ingredients safe on the skin may not be safe in the eye.

c. "If condition worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician."

d. "Do not use on children under 2 years of age except under the advice and supervision of a physician."

e. For products containing topical counterirritant active ingredients: "Do not apply to wounds or damaged skin," and "Do not bandage."

There may be additional or modified warnings which are specifically considered in the discussions of the individual active ingredients described elsewhere in this document.

4. *Labeling descriptive of product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC external analgesic drug products, as long as these terms do not imply that any therapeutic effect occurs. These terms pertain to product attributes or to the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive (in some cases, active) ingredients included in the final product formulation. Such product characteristics appear in the labeling to inform the consumer of them or to make the product appealing to the consumer, but the terms must be carefully chosen so that they do not imply any therapeutic effect.

The use of colors in pharmaceutical preparations has a long history (Ref. 4). The symbolism of color may date back to the days of the Chinese physician-

priests who noted that the color of the tongue as an indicator of disease. The Egyptians associated the vital properties of blood with its red color. Thirteenth century apothecaries used colored medicine bottles as displays. Even today rosy cheeks are associated with health. Such phrases as "creamy white," "golden lotion," "lustrous," and even "colorless" have been used to describe the coloration or lack of coloration of OTC topical drug products. Many standard coloring agents are officially recognized in the compendia, attesting to the acceptability of the practice by the medical and pharmaceutical communities.

The use of medicinal odors has been associated with the practice of medicine and pharmacy since the beginnings of recorded history (Ref. 4). The burning of leaves, sulfur, hair, feathers, and the wearing of odorous amulets were believed to drive out evil spirits which cause disease. The odor of a patient's breath has been and is still used as a diagnostic tool.

Although many chemical and instrumental methods are used to assess and measure odor, the cosmetic and pharmaceutical industries often rely on the personal reactions of human subjects in making such assessments and measurements (Ref. 4). Individuals can be trained to recognize standard reference odors and their intensity. They are then given various test formulations to evaluate and to describe in standard reference terms. Good reproducibility indicates well-trained experts. In this way, medicinal essences are blended like fine perfumes. In describing odors, such words as "aromatic," "etherlike," "camphoraceous," "acrid," and "chocolate-like" have been used by the official compendia. Some pharmaceutical companies use such phrases as "mild lemon-grass fragrance," "pleasantly scented," and "no tell-tale odor" to describe the odor or lack of odor of their particular drug products. The presence of medicinal essences in the official compendia attests to the acceptability of the practice by the medical and pharmaceutical communities.

By far the most abundant and diverse claims, with respect to the sensual attribute of an OTC external analgesic drug product, pertain to the sense of touch. Many times these attributes are associated with the physical characteristics of the vehicle. If a vehicle is soluble in water, phrases such as "greaseless," "water washable," and "not oily or sticky" are used to inform the consumer that the product is not messy. Light creams and lotions that are applied with a minimum of rubbing are ideal for application to skin lesions where inunction would result in further irritation or pain, e.g., sunburns. Phrases such as "vanishing cream base," "spreads on evenly," and "easy to apply" have been used to describe the ease of application of OTC external analgesic drug products.

In addition to the physical properties of the vehicle, there are sensations, resulting from the inclusion of certain ingredients in topical drug formulations, that provide a beneficial effect. The application of certain aromatic substances and volatile bases provide what can best be called a cooling and soothing sensation. Because of a strong psychological and emotional component, these effects are difficult to define and describe. It is the Panel's opinion that by using these sensations to distract from the patient's sensation of pain, the patient's subjective response can be favorably modified.

The Panel concludes that certain labeling claims are reasonable and informative to the consumer when they accurately reflect inherent characteristics of the marketed product. Terms such as "nongreasy," "does not stain," "soothing," "does not burn or stain," "soothing ingredients," "cooling action," "soothing or cooling relief," "penetrating relief," "provides warming relief," "for cool comforting relief," "warm comforting relief," "penetrating cooling action," "warmth that penetrates to soothe," and "soothes itching and burning" are considered acceptable in labeling. However, the Panel emphasizes that these terms should not be identified as indications for use. They are merely factual statements related to product performance. Other terms, such as "warm relief" or "soothing relief," not associated with the indications may also be included on the principal display panel.

5. *Labeling descriptive of product performance.* The Panel finds it unacceptable to use any claims related to product performance unless they can be substantiated by scientific data. Any claims, i.e., "fast," "quick," "long acting," "remarkable," etc. are considered to be misleading and may be confusing to the consumer unless they can be supported by adequate scientific data.

6. *Claims deferred to other Panels.* The following labeling claims have been deferred to other Panels since these claims are not within the scope of this Panel: "discourages infection," "helps prevent infection," "first aid," "kills germs," "chest cold discomfort," and "eases inflammation accompanying ingrown toenail."

References

(1) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 895–896, 1977.

(2) Wale, J. P., "Tidy's Massage and Remedial Exercises in Medical and Surgical Conditions," The Williams and Wilkens Co., Baltimore, pp. 18, 1961.

(3) Licht, S., "Manipulation and Traction," Waverly Press, Baltimore, 1960.

(4) Burlage, H. M., C. O. Lee, and L. W. Rising, "Other Pharamaceutical Adjuncts," *in* "Physical and Technical Pharmacy," McGraw-Hill Book Co., New York, pp. 645–686, 1963.

J. Principles Applicable to Combination Products

The Panel disagreed on principles applicable to combination products. Accordingly, this section consists of a majority report and a minority report. The minority report reflects the opinion of two Panel members.

1. *Majority report on principles applicable to combination products*—a. *General comments.* In reviewing OTC external analgesic drug combinations in the marketplace, the Panel applied the OTC Drug Review regulation (21 CFR 330.10(a)(4)(iv)) which states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel not only concurs with, but strongly supports this regulation, and believes that each active ingredient in a combination product must contribute to the claimed effect, and that the combination must provide rational concurrent therapy. It is the view of the Panel that it is irrational to use a combination product unless each of its active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination of ingredients is recommended. The specific combination should be at least as safe and effective as therapeutic doses of the individual active ingredients when used alone.

The Panel considered two major groups of combination products, i.e., combinations of ingredients that depress cutaneous sensory receptors (anesthetics, analgesics, and antipruritics), and combinations of

ingredients that stimulate cutaneous sensory receptors (counterirritants).

Below are proposed standards for combinations for all the ingredients reviewed, together with certain elaborations and reasons upon which the proposed standards are based.

OTC products containing safe and effective single active ingredients are preferred to those having multiple active ingredients. Products containing a single active ingredient reduce the possibility for occurrence of toxic, allergic, and idiosyncratic reactions, and possible unrecognized and undesirable drug interactions. It is the consensus of the Panel, therefore, that OTC external analgesic products ideally should contain only one active Category I ingredient of a particular pharmacologic class and such inactive ingredients as are necessary for pharmaceutical formulation.

Despite the idealistic situation stated above, the Panel is strongly convinced that there is a need for combination products. This conclusion is based on the premises that there is a target population for whom combination products are rational therapy, that few ingredients act exactly the same, and that external analgesic combination products have an extensive marketing history.

The Panel is aware of the lack of controlled studies in the area of use of external analgesics. Controlled clinical studies are difficult to perform for symptoms that are frequently fleeting and usually self-limiting, and the Panel is especially aware that it would be almost impossible to interest investigators in such studies. On the basis of its expertise in this area, the Panel concludes that the combinations described below are acceptable.

The Panel concludes that in the groups of combinations described below, a contribution is made by every ingredient and that the attributes added to the combination by the various ingredients enhance the product's effectiveness and convey a noticeable benefit to the consumer.

The Panel considered a highly diversified group of ingredients. Even though many are qualitatively similar in pharmacologic action, they are, in most instances, quantitatively different. The Panel has made four subdivisions of each of the two major groups (stimulate skin receptors (I), depress skin receptors (II)). Their unique characteristics are described.

The breakdown into chemical and pharmacological subclasses allows a selection of ingredients working presumably on different receptor sites to provide a variegated response not possible with a single ingredient. Combining two drugs that act at different receptor sites, as for example a "caine" type drug and an alcohol type of topical anesthetic, may result in summation (of the mixture combination) instead of addition, and the effect might be greater than that produced if each ingredient were used alone. In other words, instead of a $1 + 1 = 2$ effect, a $1 + 1 = 3$ or 4 effect could result.

Combining two topical anesthetics that act by stabilization of the nerve membrane, such as the "caine" type drugs and their pharmacological counterparts (dyclonine, pramoxine, etc.), results in an additive effect. Adriani and Zepernick (Ref. 1) showed that if half of a dose of lidocaine that causes central nervous system excitation manifested by seizures is combined with half of the dose of tetracaine that does the same intravenously, the two act additively and cause seizures. They also showed that when equal volumes of aqueous solutions of lidocaine and tetracaine are combined in concentrations that produce the maximal topical effect on the mucous membranes beyond which no further benefit is gained by increasing the concentration, the duration of action of the combination is that of the longer lasting drug. Combining the two does not further increase the duration of anesthesia.

b. *Groups and subgroups of external analgesics.* The Panel has identified four separate chemical and/or pharmacologic groups of counterirritants which provide four qualitatively different types of irritation. The Panel believes it is rational and appropriate to provide the opportunity to utilize at least two different such effects to operate when greater potency is required. The more potent counterirritants are grouped together (IA). IB is made up of drugs that provide cooling, warmth, and tingling sensations which stimulate the skin and provide organoleptic properties. Two drugs which cause vasodilatation are grouped as IC; and the capsaicin derivatives (ID) provide counterirritation probably close in potency to IA but without rubefacient properties.

The nitrogen-containing local anesthetics (IIA) that block the nerve conduction are chemically similar; they are amines. The "caine" type drugs, also IIA, tend to resemble each other chemically and are generally more effective pharmacologically but also more toxic than those drugs resembling them in structure. The hydroxy compounds (IIB) behave in the same pharmacologic manner as the nitrogen-containing drugs, yet their effectiveness and toxicities are different.

The antihistamines (IIC) not only block one of the mediators of inflammation (histamine) but also are mildly anesthetic. The salicylates (IID) whose action is not known, are grouped together as a natural chemical group.

The Panel recognizes that ingredients within the same pharmacologic group may not necessarily have the same potency or produce the same sensation (i.e., soothing, cooling, or warming effect). Because the sensations and potencies may differ, each ingredient may be characterized by its own effect or clinical impression and thus be placed into certain subgroups, or types summarized in the following table:

Groups and Subgroups of External Analgesic

Groups and subgroups	Characteristics of subgroup
I. Counterirritants (Stimulate cutaneous sensory receptors).	....
A. Allyl isothiocyanate, Ammonia water, Methyl salicylate, Turpentine oil.	Cause redness, irritation, and are relatively more potent than other commonly used counter-irritants.
B. Camphor, Eucalyptus oil, [1] Menthol.	Produce cooling sensation and have organoleptic properties.
C. Histamine dihydrochloride, Methyl nicotinate.	Vasoactive substances, vasodilators.
D. Capsaicin, Capsicum, Capsicum oleoresin.	Produce irritation without rubefaction, although approximately equal in potency to Group A ingredients.
II. Analgesics, anesthetics, antipruritics (Depress cutaneous sensory receptors).	....
A. Benzocaine, Butamben picrate, Cyclomethycaine sulfate, [1] Dibucaine, Dibucaine hydrochloride, Dimethisoquin hydrochloride Dyclonine hydrochloride, Lidocaine, Lidocaine hydrochloride, Pramoxine hydrochloride, Tetracaine, Tetracaine hydrochloride.	All have similar chemical structure, pharmacologic action, and common precursors.
B. Benzyl alcohol, Camphor, Camphorated metacresol, [1] Chlorobutanol, [1] Eugenol, [1] Hexylresorcinol, [1] Juniper tar, Menthol, Phenol, Resorcinol, Sodium phenoxide, Thymol [1].	Alcohols (hydroxyl-group), a ketones.
C. Diphenhydramine hydrochloride Methapyrilene hydrochloride Tripelennamine hydrochloride.	Antihistamines
D. Aspirin, [1] Glycol salicylate, [1] Salicylamide, [1] Triethanolamine salicylate.	Salicylic acid derivatives

[1] Indicates ingredient is classified in Category III. All oth ingredients are classified in Category I.

c. *Permitted combinations of Categor I ingredients*—(1) *Permitted combinations of active ingredients that stimulate cutaneous sensory receptors (counterirritants)*—(i) One Category I active ingredient from any subgroup of the active ingredients that stimulate

cutaneous sensory receptors (counterirritants) may combined with one, two, or three other active ingredients that stimulate cutaneous sensory receptors, provided that each active ingredient is from a different subgroup.

(ii) Camphor and menthol together (subgroup B) may be combined with one, two, or three active ingredients, provided that each other active ingredient is from a different subgroup.

(2) *Permitted combinations of active ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, antipruritics)*—(i) One Category I active ingredient from subgroup A may be combined with any one Category I active ingredient from subgroup B.

(ii) One Category I active ingredient from subgroup B may be combined with any one Category I active ingredient from subgroup C.

(iii) Any three Category I active ingredients from subgroup B may be combined, as long as two of the three are camphor and menthol.

(iv) Any one active ingredient from subgroup D that is classified as Category I may be combined with one Category I ingredient from subgroup A or subgroup B.

(3) *Permitted combinations of external analgesic active ingredients with other externally applied ingredients.* One Category I external analgesic active ingredient that depresses cutaneous sensory receptors or a Category I combination of such ingredients may be combined with a Category I skin protectant active ingredient, or with a Category I skin protectant combination, and/or a Category I antimicrobial active ingredient or with a Category I antimicrobial combination.

d. *Standards for Category II combination products*—(1) Combinations containing a Category II external analgesic ingredient are classified as Category II.

(2) Any combination product containing hydrocortisone or hydrocortisone acetate and other active external analgesic ingredients is classified as Category II.

(3) Combinations containing Category I external analgesic active ingredients combined with any active ingredient not reviewed by this or other OTC Advisory Review Panels, or having been reviewed by another OTC Advisory Review Panel and found to be either unsafe or ineffective or considered to be an irrational combination, are classified as Category II.

(4) Combinations containing any external analgesic active ingredient and a sunscreen active ingredient are classified in Category II. Such combinations are considered to be unsafe because the external analgesic active ingredient may mask the symptoms of overexposure to the sun.

(5) Combinations containing Category I external analgesic active ingredients which depress cutaneous sensory receptors (topical analgesics, anesthetics, and antipruritics) combined with any Category I external analgesic which stimulates cutaneous sensory receptors (counterirritant) are classified in Category II. It is irrational to combine such ingredients because they act in opposition to each other.

(6) Combinations containing any Category I counterirritant combined with a skin protectant as an active ingredient are classified in category II. Protectants act in opposition to counterirritant ingredients and may nullify their analgesic effect.

e. *Standards for Category III combination products*—(1) Combinations containing a Category III external analgesic active ingredient are classified in Category III.

(2) Any Category I combination listed above containing external analgesic active ingredients at less than the minimal effective dose is classified in Category III for effectiveness.

(3) Combinations containing a Category I external analgesic from subgroup A of the external analgesics that depress cutaneous sensory receptors and a Category I ingredient from subgroup C of that same group are classified as Category III for effectiveness.

2. *Minority report on principles applicable to combination products*—a. *General comments.* The minority of the Panel disagrees with the standards for combination products containing external analgesic active ingredients recommended by the majority of the Panel. The minority presents its standards for Category I, Category II, and Category III combination products below including general comments on the justification for these standards.

In reviewing OTC external analgesic drug combinations in the marketplace, the Panel bore in mind the OTC Drug Review regulation (21 CFR 330.10(a)(4)(iv)) which states:

An OTC drug may combine two or more safe and effective ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

Members of the minority concur with the basic concepts embodied in this regulation, that each active ingredient in a combination product must contribute to the claimed effects and that the combination must provide rational concurrent therapy. They believe that it is irrational to use a combination product unless each active ingredient contributes to the effective treatment of at least one of the labeled symptons for which the combination of ingredients is recommended.

The Panel considered two major groups of combination products, i.e., combinations of ingredients that depress cutaneous sensory receptors (anesthetics, analgesics, and antipruritics), and combinations of ingredients that stimulate cutaneous sensory receptors (counterirritants).

The minority has outlined below the proposed standards for combinations for all the ingredients reviewed. Also included are their elaborations and reasons for disagreeing with the majority on the proposed standards for the combination of analgesics, anesthetics, antipruritics, and counterirritants with each other and with other classes of ingredients.

It is accepted medical practice to use only drugs that are necessary to safely and effectively treat a patient. In most cases, single entity ingredients suffice to treat a particular sympton or disease entity. The minority of the Panel sees no reason why this concept is not equally applicable to self-medication with OTC products. In fact, the consumer is at a disadvantage because he or she is self-treating symptoms with OTC products without a physician's advice.

OTC products containing single safe and effective active ingredients are therefore preferred to those having multiple active ingredients. Products containing a single active ingredient reduce the possibility of the occurrence of toxic, allergic, and idiosyncratic reactions, and possible unrecognized and undesirable drug interactions. This is the case when a drug is prescribed by a physician and should also be the case when a drug is used by a layman for self-treatment. Therefore the Panel minority believes that OTC external analgesic products should contain only one active Category I ingredient of a particular pharmacologic class to treat a particular indication and such inactive ingredients as are necessary for pharmaceutical formulation.

The minority of the Panel is familiar with the concept that is sometimes

proposed, that subtherapeutic doses of active ingredients of the same pharmacologic class may be combined for treating a particular indication provided that the resulting combination is as safe and effective as each individual ingredient would be when used alone in full therapeutic doses. For example, if drug A and drug B, each of which has a similar pharmacologic activity, are combined at half of their usual therapeutic doses, the combination AB must be as safe and effective as drug A or drug B used alone in full therapeutic doses. Neither safety nor effectiveness is compromised by allowing this combination.

This concept appears plausible and has considerable appeal, at least theoretically. The concept may be applicable to some ingredients reviewed by some OTC Panels. However, there is a paucity of data supporting the application of this concept to external analgesics. Actually, there is considerable evidence that the contrary is true. Although the pharmacologic responses of all the topical anesthetics and analgesics reviewed by the Panel are qualitatively similar, each drug is quantitatively different. Whether the hydroxy type of topical analgesics act in consort when combined with the nitrogenous type of anesthetics and to what degree they may do so is not known. Valid data from controlled studies are not available. The pharmacologic activities of anesthetics, such as periods of latency, duration of action, and degree of blockade vary widely since they are dependent on their oil-water partition coefficients, protein-binding power, erythrocyte plasma distribution ratio, surface tension lowering effects, pKa, biologic stability in vivo, and other physical and chemical factors. These factors all vary widely with each ingredient. Reducing the concentration of a topical anesthetic in a solution that is applied to a nerve reduces the amount of the anesthetic that passes into a nerve fiber, prolongs the latent period, and shortens the duration of action. The blockade may only be partial because the fibers in a nerve differ in size. Each fiber is not blocked simultaneously, and some fibers are not blocked at all if the concentration of the anesthetic is below the minimum effective concentration (Cm) for that fiber size.

Longer lasting drugs have longer latent periods than those whose durations of action are short. It is known that if half of a minimum effective dose of a long-lasting topical anesthetic of the "caine" type is combined with half of a minimum effective dose of a short-acting topical anesthetic of the same type, no blockade occurs, or if it occurs, it is incomplete. The minimum effective concentration of each ingredient must be combined to obtain an effective blockade. Thus, combining two "caine" type topical anesthetics at half the therapeutic concentrations does not follow the A+B concept mentioned above. Combining two topical anesthetics at their minimum effective concentrations usually results in a duration of action equal to that of the longer-lasting drug when that drug is used alone. The period of latency will be the same as that of the shorter acting drug if that drug were used alone. Nothing of significance is gained from a therapeutic standpoint by combining the two topical anesthetics. In addition, safety is compromised because the potential for toxicity is increased by combining the two drugs at full therapeutic doses. This is not in conformity with the principles as mandated in OTC Drug Review regulations 21 CFR 330.10(a)(4)(iv).

These facts have been verified by testing these drugs on mucous membranes. However, since topical anesthetics behave similarly at different sites of the body, there is little reason to believe that they do not behave in the same manner on the skin. There is a paucity of data derived from controlled studies concerning periods of latency or duration of action of topical anesthetics on the skin. Such data are not available for single entity ingredients, let alone combinations of two or more ingredients. The minority of the Panel finds no valid reason for combining two effective topical anesthetics or analgesics. Since the actions of topical anesthetic ingredients are diverse, and they differ from each other quantitatively in their responses, single ingredients can be selected to meet the desired therapeutic need, i.e., a short-acting drug may be selected when a short action is desired and a long-acting drug may be selected when long duration is desired.

More strenuous objections can be raised for combining two or more counterirritants (analgesics) than for combining two or more topical anesthetics. Although effectiveness is an important consideration, these objections are based largely on safety considerations. The counterirritants are a heterogenous group of chemicals that are irritating to the skin. They do not fall into well-delineated chemical families, as do the analgesics and anesthetics. Counterirritants act by inducing a temporary reversible inflammatory response on the skin and by inciting sensory cutaneous receptors to exert their claimed effect. The minority of the Panel cannot concur with the statement of the majority that "The Panel has identified four separate chemical and/or pharmacologic groups of counterirritants which provide four qualitatively different types of irritation." No valid data are available to support this concept. Irritation is irritation and the apparent different types assumed to exist by the majority are the result of variations in response of the skin that depend upon such factors as dosage, sensitivity, or responsiveness of the skin of an individual to a drug, duration of contact, and various other factors. The minority, therefore, believes that the majority cannot justify delineating four types of irritation (Ref. 2).

In both its introductory statement and in the ingredient evaluation statements elsewhere in this document, the majority has emphasized that these drugs are hazardous, and unless used cautiously and according to directions, cause damage to the intact skin. It has also emphasized, in its introductory statement on counterirritants, that counterirritant ingredients that are the least readily absorbed from the skin are most desirable for clinical use. (See part II. paragraph F.4. above—Topical counterirritants.) The majority of the Panel has proposed special warnings in the labeling for the use of counterirritants. There are no data from controlled studies indicating that the A+B concept described above can be applied to counterirritants, and there are no data from controlled studies on the additive effects or possible synergistic effects when counterirritants are combined. Such additive effects may enhance toxicity more than efficacy and impair safety. Furthermore, some counterirritant ingredients are not single chemical entities but are unrefined mixtures of organic substances, such as oleoresins, terpins, resins, and other chemicals. Some counterirritants are distillates of wood and other raw materials of botanical origin. Thus, a combination supposedly composed of two or more single entity counterirritant ingredients could consist of many ingredients. The minority of the Panel finds no well-documented scientific justification for combining two or more effective counterirritants. Counterirritant ingredients have received little attention from clinical investigators in recent years. In fact, these ingredients are not mentioned in the majority of present-day textbooks on pharmacology and therapeutics.

The Panel recognizes that many combinations of external analgesics.

particularly the counterirritants, have been on the market for many years. The counterirritants continue to be used by the laity for the symptomatic relief of pain of muscle and joints; however, their use for these conditions has been supplanted mostly by other methods of treatment by the medical profession.

The minority of the Panel feels that neither the OTC drug review regulations nor the historical evidence for the use of these combination products support the concept that the long-time use of an OTC product, with apparent beneficial results based on clinical observations by consumers, or without complaints of adverse reactions, attests to their safety and effectiveness. The minority of the Panel is not impressed by statements appearing in manufacturer submissions, such as "marketing experience has been favorable" or "no complaints have been reported," etc. Although the Panel minority considers marketing experience data and frequency of customer complaints to be of interest, it does not consider such data to be the type of proof that is valid for establishing safety and efficacy in a scientific review of standards of existing OTC products. The paucity or lack of reports of adverse reactions are merely negative findings, and negative findings obtained from marketing data do not constitute a sound basis for establishing a product's safety and efficacy. Furthermore, none of the submissions describe the manner in which the data were collected from the users of these products, the instructions provided to the users to facilitate and assure that all the necessary and meaningful data would be forthcoming in reporting adverse reactions, and the manner in which collection of such data was monitored. None of the submissions describe by whom the data were interpreted, or otherwise explain pertinent, significant details concerning their methods of adverse reaction reporting. The minority of the Panel, therefore, does not concur with the opinion of the majority of the Panel that the use of analgesic combinations is justified because such combinations have an extensive marketing history.

The minority of the Panel recognizes that it may have overlooked or may otherwise be unaware of data concerning combinations of external analgesic ingredients on the marketplace that provide therapeutic advantages not possessed by single entity Category I ingredients. It is not the intent of the Panel minority to deprive the public of the benefits of the use of such combinations if they do, indeed, exist and provide effective rational therapy. The minority of the Panel, therefore, recommends that a combination of two Category I active ingredients with the same pharmacologic activity be allowed if it is known, or has been shown, that the combination is as safe and effective as doses of the individual active ingredients alone and that the combination provides some well defined therapeutic advantage that neither ingredient provides when used alone and not in combination.

The term "therapeutic advantage" does not indicate that the combination is expected to be pharmacologically superior to each ingredient. It does indicate, however, that combining the ingredients provides a therapeutic effect that is beneficial for treating the claimed symptoms not provided for by using the individual ingredients alone. Combinations of ingredients meeting these stipulations should be classified as Category I. If it is not known or it has not been shown that the foregoing stipulations concerning safety, effectiveness, and therapeutic advantage have been met, the minority of the Panel recommends classification of such a combination as Category III. It is the opinion of the minority of the Panel that if no therapeutic advantage is gained by combining two ingredients of the same pharmacologic activity, the possibility of toxic, allergic, and idiosyncratic reactions is increased, as mentioned above, and safety is compromised.

The minority of the Panel is puzzled by the comment of the majority of the Panel when it states that:

> It is the consensus of the Panel, therefore, that OTC external analgesic products ideally should contain only one active Category I ingredient of a particular pharmacologic class and such inactive ingredients as are necessary for pharmaceutical formulation.
>
> Despite the idealistic situation stated above, the Panel is strongly convinced that there is a need for combination products. This conclusion is based on the premises that there is a target population for whom combination products are rational therapy, that few ingredients act exactly the same, and that external analgesic combination products have an extensive marketing history.

The majority of the Panel agrees with the minority that only one Category I active ingredient of a pharmacologic class is necessary; yet the majority of the Panel contradicts this established medical principle by stating that it is strongly convinced that "there is a need for combination products." There is no data from controlled studies to substantiate that there is such a need upon which the Panel can base its conclusions. The minority of the Panel finds no supporting data in the entire OTC review of topical external analgesics that identify the target population mentioned for whom such a need exists.

The majority of the Panel states, "The Panel is aware of the lack of controlled studies in the area of use of external analgesics. Controlled clinical studies are difficult to perform for symptoms that are frequently fleeting and usually self-limiting, and the Panel is especially aware that it would be almost impossible to interest investigators in such studies. On the basis of its expertise in this area, the Panel concludes that the combinations described below are acceptable."

On the one hand, the majority of the Panel admits that there is a lack of meaningful data from controlled studies on the use of external analgesics. On the other hand, the majority of the Panel concludes on the basis of its expertise, but without supporting data, that the combinations it describes in its combination principles are acceptable. The minority of the Panel is unable to reconcile these opposing and contradictory views expressed by the majority of the Panel.

The minority of the Panel agrees with the following conclusions of the Commissioner, published in the **Federal Register** of November 12, 1973 (38 FR 31261), concerning difficulties in performing controlled clinical studies to determine the safety and effectiveness of OTC drug products:

> The Food and Drug Administration recognizes that OTC drug studies are often more difficult to undertake than those involving prescription drugs. OTC drug studies are principally concerned with measuring symptomatic relief, requiring methods that are more subjective than those used to measure the resolution of a disease condition. In all cases, however, such tests are entirely feasible and, indeed, have in many cases been conducted in the past. Nor is difficulty in performing studies sufficient justification for retaining on the market drugs the safety and effectiveness of which are inadequately documented.

The minority of the Panel also disagrees with the assumptions made by the majority in its conclusion that "in the groups of combinations described * * * a contribution is made by every ingredient and that the attributes added to the combination by the various ingredients enhance the product's effectiveness and convey a noticeable benefit to the consumer." The minority cannot support these contentions. There is no scientific data in the literature or in the submissions upon which to base such generalizations regarding either the

contribution made by every ingredient in a combination or the "attributes" added to a combination to enhance a product's effectiveness.

On the basis of its evaluation of the majority's combination principles, the minority of the Panel concludes that two active ingredients with the same pharmacologic activity, i.e., two active ingredients that stimulate cutaneous sensory receptors, e.g., two topical counterirritants, may be combined when the conditions concerning safety, efficacy, and therapeutic advantage are met as discussed above.

b. *Standards for Category I combination products*—(1). Each active ingredient and its labeling in a combination product must be generally recognized as safe and effective (Category I).

(2) One Category I external analgesic active ingredient that depresses cutaneous sensory receptors may be combined with one external nonanalgesic Category I active ingredient, e.g., skin protectant, at a dosage range between its minimum effective dosage and maximum allowable dosage, provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations," and "for the temporary relief of minor skin irritations and itching."

(3) One Category I external analgesic active ingredient that depresses cutaneous sensory receptors may be combined with one Category I antimicrobial active ingredient or with a Category I antimicrobial combination.

c. *Standards for Category II combination products*—(1) Combination products containing a Category II external analgesic ingredient or Category II labeling are classified as Category II.

(2) Combinations of three or more external analgesic active ingredients are classified as Category II because it is irrational to use more than one safe and effective ingredient to treat one labeled symptom for which the combination is intended.

(3) Any combination product containing hydrocortisone or hydrocortisone acetate and other active external ingredients is classified as Category II. The safety of hydrocortisone combinations for OTC use has not been established. At present, hydrocortisone combinations are available for use by prescription only.

(4) Combination products containing Category I external analgesic active ingredients combined with any active ingredient(s) not reviewed by this or other OTC Advisory Review Panels or found to be either unsafe or irrational are classifed as Category II.

(5) Combination products containing any external analgesic active ingredient and a sunscreen active ingredient are classified as Category II. Such combinations are considered to be unsafe because the external analgesic active ingredient may mask the symptoms of overexposure to the sun.

(6) Combination products containing Category I external analgesic active ingredients which depress cutaneous sensory receptors (topical analgesics, anesthetics, and antipruritics) combined with any Category I external analgesic which stimulates cutaneous sensory receptors (counterirritant) are classified in Category II. It is irrational to combine such ingredients because they act in opposition to each other. Such combinations are not only irrational but may also be unsafe.

(7) Combination products containing any Category I counterirritant combined with a skin protectant are classified as Category II. Protectants act in opposition to counterirritant ingredients and nullify their analgesic effect.

d. *Standards for Category III combination products*—(1) Combination products containing a Category III external analgesic active ingredient and no Category II external analgesic active ingredient or labeling are classified as Category III.

(2) Combination products containing two Category I external analgesic active ingredients are classified as Category III. It will have to be known or have to be shown that each active ingredient makes a contribution to the claimed effect and that the conditions concerning efficacy, therapeutic advantage, and safety described above are met.

References

(1) Adriani, J. and R. G. Zepernick, "Comparative Potency and Duration of Action of Topical Anesthetic Drugs in Man," *Anesthesiology*, 24:120–121, 1963.

(2) Cushny, A. R., "A Textbook of Pharmacology and Therapeutics, " 7th Ed., Lea and Febiger, Philadelphia, pp. 197–198, 1918.

II. External Analgesics

A. Summary of the Categorization of Active Ingredients

The Panel has summarized its categorization of active ingredients in the table below.

Active ingredients that have been evaluated and found to be generally recognized as safe and not effective for OTC use are classified in Category I. Active ingredients that have been evaluated and found not to be generally recognized as safe and effective are classified in Category II. Those active ingredients for which the available data are insufficient to permit final classification at this time have been classified in Category III. In addition, the Panel has grouped external analgesic active ingredients by their pharmacologic activity as either depressors of cutaneous sensory receptors (anesthetics, analgesics, and antipruritics) or stimulators of cutaneous sensory receptors (counterirritants).

Categorization of External Analgesic (EA) Active Ingredients

Active ingredient	EA that depress cutaneous sensory receptors	EA that stimulate cutaneous sensory receptors
Allyl isothiocyanate	(1)	
Ammonia water, stronger	—	
Aspirin	III [2]	—
Benzocaine	I	—
Benzyl alcohol	I	—
Butamben picrate	I	—
Camphor	I	
Camphorated metacresol	III	—
Capsaicin	—	
Capsicum	—	
Capsicum oleoresin	—	
Chloral hydrate	II	II
Chlorobutanol	III	—
Cyclomethycaine sulfate	III	—
Dibucaine	I	—
Dibucaine hydrochloride	I	—
Dimethisoquin hydrochloride	I	—
Diphenhydramine hydrochloride	I	—
Dyclonine hydrochloride	I	—
Eucalyputus oil	—	II
Eugenol	III	—
Glycol salicylate	III	—
Hexylresorcinol	III	—
Histamine dihydrochloride	—	
Hydrocortisone	(3)	—
Hydrocortisone acetate	(3)	—
Juniper tar	I	—
Lidocaine	I	—
Lidocaine hydrochloride	I	—
Menthol	I	
Methapyrilene hydrochloride	I	—
Methyl nicotinate	—	
Methyl salicylate	—	
Phenol	I	—
Phenolate sodium	I	—
Pramoxine hydrochloride	I	—
Resorcinol	I	—
Salicylamide	III	—
Tetracaine	I	—
Tetracaine hydrochloride	I	—
Thymol	III	—
Triethanolamine salicylate	III	—
Tripelennamine hydrochloride	I	—
Turpentine oil	—	

[1] The (—) symbol indicates an unacceptable pharmacologic activity for the ingredient.

[2] All ingredients classified as Category III were done so fo effectiveness considerations except for camphorated metacresol which was classified as Category III for safety and effectiveness considerations.

[3] Hydrocortisone and hydrocortisone acetate are external analgesics only for use as topical antipruritics.

B. Categorization of Data

1. *Category I conditions under which external analgesic ingredients are generally recognized as safe and effective and are not misbranded.*

The Panel recommends that the Category I conditions be effective 30

days after the date of publication of the final monograph in the Federal Register.

Category I Active Ingredients

Allyl isothiocyanate
Ammonia water, stronger
Benzocaine
Benzyl alcohol
Butamben picrate
Camphor
Capsicum preparations
  Capsaicin
  Capsicum
  Capsicum oleoresin
Dibucaine
Dibucaine hydrochloride
Dimethisoquin hydrochloride
Diphenhydramine hydrochloride
Dyclonine hydrochloride
Histamine dihydrochloride
Hydrocortisone preparations
  Hydrocortisone
  Hydrocortisone acetate
Juniper tar
Lidocaine
Lidocaine hydrochloride
Menthol
Methapyrilene hydrochloride
Methyl nicotinate
Methyl salicylate
Phenol
Phenolate sodium
Pramoxine hydrochloride
Resorcnol
Tetracaine
Tetracaine hydrochloride
Tripelennamine hydrochloride
Turpentine oil

a. *Allyl isothiocyanate.* The Panel concludes that allyl isothiocyanate is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Allyl isothiocyanate, also known as volatile oil of mustard, is a colorless or pale yellow liquid with a very pungent, irritating odor and acrid taste. It is slightly soluble in water, and miscible with alcohol and most organic solvents. Its chemical formula is C_4H_5NS (Ref. 1).

Allyl isothiocyanate is derived from the powdered seeds of *Brassica nigra* (Black Mustard) and other species of mustard, or prepared synthetically by the reaction of allyl iodide and potassium thiocyanate.

Allyl isothiocyanate does not occur naturally in mustard seed. Instead, mustard seed contains a fixed oil, a glycoside (sinigrin), and the enzyme myrosin. In order to produce the volatile oil, the fixed oil must first be removed. Following this, the residue of dried powdered seed is moistened with warm water, and hydrolysis of the sinigrin occurs, yielding allyl isothiocyanate.

Poultices employing powdered mustard seed have been used as a counterirritant for many years. Mustard plaster, National Formulary XI, was actually a poultice prepared by applying powdered mustard seed, deprived of its fixed oil, with a suitable adhesive to cloth or paper at a concentration of 2.5 g/100 cm^2. The poultice is moistened in tepid water before applying to the intact skin, and the body temperature of the patient supports the ongoing enzymatic production of the volatile oil, allyl isothiocyanate (Ref. 2).

(1) *Safety.* Clinical use has confirmed that allyl isothiocyanate is safe in the dosage range used as an OTC external analgesic.

Black mustard is mentioned by Diocletian (300 A.D.) as a condiment, and both Theophrastus and Pliny mention its use in medicine (Ref. 3). Mustard is used chiefly as a condiment. In large quantities it causes violent irritation of the stomach and bowel, with vomiting, acute pain, purging and tenderness in the abdomen, and collapse. Mustard in warm water was formerly used as an emetic in cases of poisoning (Ref. 4). Small doses taken orally may increase apetite, stimulate secretion of digestive ferments, and increase peristalsis. Placed on the tongue, mustard causes prickling and burning. If swallowed, these effects occur in the throat and stomach (Ref. 5).

Dogs injected with 0.01 milliliter/kilogram (ml/kg) experienced a fall in blood pressure due to direct depression of the vasomotor center. The heart is alternately accelerated and slowed, and heart block may occur as the ventricles are more poisoned than the auricles. Death commonly occurs in mammals from respiratory paralysis before the heart is profoundly affected (Ref. 5).

Jenner et al. administered a 10-percent concentration of allyl isothiocyanate in corn oil to rats by intubation. After 2 weeks of observation, the LD_{50} was found to be 339 milligrams/kilogram (mg/kg) (Ref. 6).

In high concentration, volatile oil of mustard is rapidly absorbed from intact (unbroken) skin as well as from all mucous membranes. Penetration of the skin is rapid and, if not removed soon after application, it may cause ulceration (Ref. 5). Used as a poultice, erroneously termed a mustard plaster, the allyl isothiocyanate released by the presence of water may cause the infalmmatory action to go beyond erythema to vesication (Ref. 7).

Marketing experience has been good, with no reports of adverse reactions serious enough to require treatment in a user pupulation (Ref. 8). The safety of allyl isothiocyanate has been demonstrated by marketing data. Over the period 1962 to 1972, inclusive, nearly 15,500,000 package units were manufactured and marketed. Over this 11-year period, 43 letters of minor complaints were received. This represents a ratio of 1 complaint per 350,000 package units marketed. No reports of serious untoward effects were received (Ref. 8).

It is the opinion of the Panel that although the actual number of adverse effects attributed to the external use of mustard preparations is relatively low, care should be taken to assure that safety is maintained through adequate packaging, labeling, and application.

(2) *Effectiveness.* There are studies documenting the effectiveness of allyl isothiocyanate as an OTC external analgesic. In addition, due to the ingredient's wide use and clincial acceptance and on the basis of published reports in the literature, the Panel concludes that allyl isothiocyanate is effective for use as an OTC external analgesic.

Allyl isothiocyanate is a powerful counterirritant (Ref. 9). Mustard plaster, listed in the National Formulary IX, is a poultice. When moistened thoroughly with tepid water and applied to the skin, the poultice produces a decided warmth and reddening of the skin within 5 minutes (Ref. 10).

Peterson et al., in their study of the response of the skin to rubefacients (Ref. 11), applied nine different rubefacients (counterirritants), including 5 percent volatile mustard oil to the skin of five human subjects. The skin of the upper back was used for the application of rubefacients ointments. Eighty milligrams (mg) of each rubefacient ointment was applied with the same technique. Thereafter, the degree of erythema and skin temperature of each site were observed at 5-minute intervals for a minimum of 30 minutes. The Sargent Thermistor unit recorded changes in skin temperature. Erythema was graded 0 to 3+, (1+ for slight erythema, 2+ for moderate, and 3+ for marked erythema). Several of the preparations evoked no erythema or temperature elevation, including 5 percent tincture of capsicum, along with tincture of cantharides, methyl salicylate, Peruvian balsam, and Unibase control. Those producing erythema and Temperature changes were nicotinic acid, tetrahydrofurfuryl ester of nicotinic acid, camphor, and volatile mustard oil. With various other rubefacients, e.g., methyl nicotinate which did produce erythema, the quantitative inunction of rubefacients ointments had little or no effect on the resultant cutaneous response of the subject. The skin temperature elevation evoked by rubefacients seems to

quantitatively parallel the extent of erythema produced.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 5.0 percent concentration of allyl isothiocyanate to affected area not more than 3 to 4 times daily. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. below—Category I labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 41, 1976.

(2) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 763–764, 1973.

(3) Claus, E., V. Tyler and L. Brady, "Pharmacognosy," 6th Ed., Lea and Febiger, Philadelphia, p. 119, 1970.

(4) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, p. 952, 1975.

(5) Solis-Cohen, S. and T. S. Githens, "Pharmacotherapeutics-Materia Medica and Drug Action," D. Appleton and Co., New York, pp. 1030–1033, 1928.

(6) Jenner, P. M., E. C. Hagan J. M. Taylor, E. L. Cook, and O. G. Fitzhugh, "Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity," *Food and Cosmetics Toxicology,* 2:327–343, 1964.

(7) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 764, 1973.

(8) OTC Volume 060051.

(9) Todd, R. G., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 1245, 1972.

(10) "The National Formulary IX," The American Pharmaceutical Association, Washington, DC, p. 342, 1950.

(11) Peterson, J. B., E. M. Farber, and G. P. Fulton, "Responses of the Skin to Rubefacients," *Journal of Investigative Dermatology,* 35:57–64, 1960.

b. *Ammonia water, stronger.* The Panel concludes that stronger ammonia water is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Stronger ammonia water is also known as Strong Ammonia Solution, National Formulary XiV. It is an aqueous solution of ammonia (NH_3) containing 27 to 30 percent weight in weight (w/w) of NH_3. Upon exposure to air, it loses ammonia rapidly. Stronger ammonia water is a colorless, transparent liquid, having an exceedingly pungent characteristic odor. It is miscible with alcohol. Even when well diluted it is strongly alkaline to litmus. It has a specific gravity of approximately 0.90.

Stronger ammonia water is a potent chemical reagent which is also used as a pharmaceutical necessity for the preparation of ammonia water by dilution. It is too strong for internal administration or topical application. The following precautionary statement is quoted from the National Formulary XIV.

Caution—Use care in handling Strong Ammonia Solution because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste Strong Ammonia Solution, and avoid inhalation of its vapor.

Ammonia (NH_3) is a colorless, transparent gas having a density approximately 0.6 that of air, an exceedingly pungent odor, and an acrid taste. The gas is described as an irrespirable gas since it is so irritating that, upon contact, it produces an immediate spasm of the glottis (Ref. 1). Ammonia is very soluble in water. A portion of the dissolved ammonia gas reacts chemically with water to form ammoniun hydroxide. Ammonia and ammonium hydroxide react with acids to form salts containing the ammonium ion (NH_4+).

Ammonium ion in many respects acts in a manner analogous to the alkaline metals and has been called the volatile alkali. However, ammonium hydroxide is only feebly basic in comparison with the true alkaline metal hydroxides and is readily displaced from its salts by alkaline metal ions. Consequently, ammonium salts and particularly the ammonium salts of fatty acids (soaps) are not as stable as the corresponding products made by reaction with alkaline hydroxides. They are also more susceptible to thermal decomposition (Ref. 2).

Ammonia liniment, National Formulary IX, is prepared by adding 250 milliliters (mL) of diluted ammonia solution to 750 mL of a mixture of oleic acid and sesame oil. A portion of the ammonia reacts with the oleic acid to form ammonium oleate which, in turn, acts as an emulsifying agent for the water and sesame oil. The concentration of ammonia in the finished emulsion is approximately 2.5 percent (Ref. 3).

(1) *Safety.* Clinical use has confirmed that stronger ammonia water is safe in the dosage range used as an OTC external analgesic.

Ammonia is a naturally occurring product found abundantly in body tissues. It has been used internally as a reflex stimulant and as a carminative in veterinary medicine (Ref. 4). The ammonium ion serves a major role in maintaining the acid-base balance of normal body fluids. The ammonia liberated from deamination of amides provides the largest portion of this ammonia balance (Ref. 5). In man the major site of ammonia disposal is in the liver, where it is converted to urea. Patients with severe hepatic disease or with portocaval shunts often have elevated blood ammonia levels and often develop derangements of the central nervous system which are manifested by disturbance of consciousness, tremor, hyperreflexia, and EEG abnormalities (Ref. 5).

The fatal dose of ammonium hydroxide by ingestion is about 30 mL of a 25-percent concentration (Ref. 6).

The symptoms of poisoning from ammonia are due to local irritation rather than caustic effects. There is severe pain in the mouth, throat, and stomach, with vomiting and gastritis (Ref. 7). Inhalation of ammonia vapor casues sneezing and coughing, and in high concentrations causes the throat to produce immediate spasm and closure of the glottis, resulting in asphyxia (Ref. 7). Ammonia and ammonium hydroxide cause extremely painful irritation of all mucous membranes (Ref. 5). However, under normal circumstances, oral administration of relatively large doses of ammonium salts produce no significant alterations or toxic effects (Ref. 8). The reflex stimulant property of dilute concentrations of ammonia serves as a valuable protective device against the accidental or voluntary ingestion of topical products containing free ammonia.

This reflex stimulant property is utilized as the basis of the use of "smelling salts," which contain ammonium carbonate in their formulation. Ammonium carbonate is a mixture of ammonium bicarbonate (NH_4HCO_3) and ammonium carbamate (NH_2COONH_4). The latter reacts with water to form the carbonate [$(NH_4)_2CO_3$],which then decomposes to release free ammonia which is the respiratory stimulant.

Aromatic ammonia spirit, National Formulary XIV, is also used as a respiratory stimulant. This product derives its activity from two constituents: ammonium carbonate 3.5 percent and strong ammonia solution equivalent to approximately 1.9 percent available ammonia. It is administered orally in small doses, or held near the nostrils for inhalation of volatile vapor.

Ammonia preparations used externally have been found in the National Formulary, United States Pharmacopeia, and British

Pharmacopeia. Marketing data of four decades have yielded few adverse reactions (Ref. 9).

(2) *Effectiveness.* Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that stronger ammonia water is effective for use as an OTC external analgesic.

Few authoritative publications provide information regarding optimum concentrations of ammonia in counter-irritant products. The Merck Index suggests a lower limit of 1 percent and an upper limit of 5 percent (Ref. 10).

Numerous formulations for liniments containing ammonia can be found in the literature. Many of these are emulsions in which an extemporaneously prepared ammonia soap serves both as an emulsifying agent and a lubricant.

Ammonia liniments, National Formulary IX, is prepared by mixing 25 percent diluted ammonia solution (equivalent to 2.5 percent ammonia) with 1 percent oleic acid and 74 percent sesame oil. The ammonia reacts chemically with the oleic acid and free fatty acids present in the sesame oil to form a soap, which serves as the emulsifying agent for the water present in the diluted ammonia solution and the sesame oil (Ref. 11).

The British ammonia liniment (Ref. 12) is prepared by combining 25 percent diluted ammonia solution (equivalent to 2.5 percent ammonia), 2.5 percent oleic acid, and 72.5 percent liquid paraffin (Ref. 13).

A number of formulas for liniments containing ammonia are found in The Pharmaceutical Recipe Book (Ref. 14). Concentrations of ammonia range from approximately 0.5 percent to 2.65 percent. An older British formulation, ammoniated almond oil lotion, contains 3.5 percent ammonia (Ref. 15). Another British formula, ammoniated liniment of camphor, contains more than 7 percent ammonia (Ref. 11).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1.0 to 2.5 percent concentration available ammonia (NH_3) to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B. 1. below—Category I Labeling.)

References

(1) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 65, 1950.

(2) Osol, A., "Remington's Pharmaceutical Sciences," 14th Ed., Mack Publishing Co., Easton, PA, p. 405, 1970.

(3) "The National Formulary IX," The American Pharmaceutical Association, Washington, DC, p. 39, 1950.

(4) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 69, 1976.

(5) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 794, 1975.

(6) Dreisbach, R. H., "Handbook of Poisoning," 7th Ed., Lange Medical Publications, Los Altos, CA, p. 187, 1971.

(7) Todd, R. G., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 85, 1972.

(8) DiPalma, J. R. "Drill's Pharmacology in Medicine," 3d Ed., McGraw-Hill Book Co., New York, p. 710, 1965.

(9) OTC Volume 060009.

(10) Stecher, P. G., "The Merck Index," 5th Ed., Merck and Co., Rahway, NJ, p. 29, 1940.

(11) Osol, A., "Remington's Pharmaceutical Sciences," 11th Ed., Mack Publishing Co., Easton, PA, p. 298, 1956.

(12) "British National Formulary," Hazell, Watson, and Viney LTD, London, p. 122, 1960.

(13) Todd, R. G. "Martindale, The Extra Pharmacopeia," 25th., The Pharmaceutical Press, London, p. 95, 1971.

(14) "The Pharmaceutical Recipe Book," 2d Ed., The American Pharmaceutical Association, Washington, DC, p. 64, 1943.

(15) Todd, R. G., "Martindale, The Extra Pharmacopeia," 25th Ed., The Pharmaceutical Press, London, p. 96, 1971.

c. *Benzocaine.* The Panel concludes that benzocaine is safe and effective for use as an OTC external analgesic as specified in the dosage section discussed below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics as described below.

Benzocaine is an effective topical anesthetic that has enjoyed widespread and long-term usage since 1903. Benzocaine was also called anesthesin, orthocesin, and parathesin. It was official for many years in the United States Pharmacopeia. Benzocaine is also listed in the National Formulary XIV. Benzocaine is the ethyl ester of aminobenzoic acid. It may be prepared by reducing paranitrobenzoic acid to aminobenzoic acid and esterifying the latter with ethyl alcohol in the presence of sulfuric acid. Benzocaine is a white, crystalline, stable powder. Benzocaine melts at 88° to 92° C. It is odorless and has a somewhat bitter taste. The powder induces a sense of numbness when placed on the tongue.

Benzocaine is one of a group of several anesthetics which is often referred to as one of the "insoluble" topical anesthetics. This group includes the propyl ester of aminobenzoic acid (risocaine), the butyl ester (butamben), and two other chemically related compounds called orthocaine and orthoform new (Ref. 1). The safety of benzocaine is due to the fact that it is poorly soluble in water. One g of benzocaine dissolves in 2,500 mL water, 5 mL alcohol, 2 mL chloroform, and 4 mL ether. Benzocaine is lipophilic and is soluble in various oils such as olive, peanut, and almond oil. It is also soluble in petrolatum, dipropylene glycol, and various polyethylene glycols. Benzocaine is stable in air. However, if boiled with hydrochloric acid, it is hydrolyzed and converted to aminobenzoic acid and ethyl alcohol. Benzocaine is a base by virtue of the amino group on the benzoic acid nucleus. Because it is lipid soluble and poorly ionized, it readily penetrates the lipid barriers of the cell membranes. Benzocaine forms salts with hydrochloride acid, picric acid, and other acids. The hydrochloride salt is irritating to the mucous membranes and to the skin.

Benzocaine has slight antiseptic and bacteriostatic actions, but these actions are not clinically significant. Benzocaine acts, as do other topical anesthetics, on the axonal membrane to interrupt conduction. Like other topical anesthetics, it stabilizes the membrane to prevent the ingress of sodium ions into the axonal cytoplasm. Its anesthetic activity is decreased or lost when formulated in an acid medium because it forms salts (Refs. 1, 2, and 3) by the interaction of acids with the amino group. The salts are ionized and do not readily penetrate the lipid barriers or cell membranes.

(1) *Safety.* Clinical use has confirmed that benzocaine is safe in the dosage range used as an OTC external analgesic.

Benzocaine is one of the most widely used and safest topical anesthetics found in OTC preparations. The domestic production is approximately 1¼ million pounds (lbs) per year. In addition, there is a quantity of benzocaine imported which adds approximately 30 percent more to the domestically produced quantity (Ref. 4). Because it has a low degree of water solubility, the quantities absorbed are relatively insignificant, and plasma levels that cause systemic reactions characteristic of the soluble "caine" type drugs and their allies do not occur with benzocaine. The convulsions and cardiac depression characteristic of the "caine" type drugs do not occur with benzocaine and reports of such reactions with the use of benzocaine are nonexistent. Blood plasma contains pseudocholinesterases which hydrolyze

and detoxify esters of aminobenzoic acid such as procaine, butethamine, and tetracaine. The exact metabolic pathway for the biodegradation of benzocaine is not known (Ref. 1). However, it is likely that benzocaine undergoes hydrolysis into aminobenzoic acid and ethanol. The ethanol is oxidized and the aminobenzoic acid is conjugated with glycine or excreted unchanged into the urine. In studies conducted in rats, benzocaine has been isolated from tissues after topical application to the skin. Traces of unmetabolized benzocaine have been detected in the urine (Ref. 5).

Benzocaine has been administered orally to relieve stomach pain without any toxic effects. It causes some discomfort by the oral route probably because it forms the hydrochloride salt. The lethal dose in man is not known, but the Panel is unaware of any fatalities due to the oral ingestion of benzocaine. Lethal doses have been determined in animals when benzocaine has been administered by various routes. Astrom and Persson determined the toxicity of benzocaine in rabbits and compared it with that of several other topical anesthetics (Ref. 6). The anesthetics were applied to various mucous surfaces by the intravesicular, intranasal, and intratracheal routes. When administered by the intratracheal route, the LD_{50} for benzocaine was 146 mg/kg; for tetracaine it was 4.4 mg/kg; for cocaine, 30 mg/kg; and for lidocaine, 75 mg/kg. When the drugs were administered intranasally, the LD_{50} for benzocaine was 104 mg/kg, compared to 10 mg for tetracaine, 50 mg for cocaine, and 135 mg for lidocaine. Using tetracaine as a reference unit of toxicity and designating this unit as 1, the toxic dosage relationships would be tetracaine 1, cocaine 6.8, lidocaine 17.1, and benzocaine 33.2 when the drugs were administered by the intratracheal route. In other words, approximately 33 times more benzocaine would be required to cause a fatal response than would be required if tetracaine were used. By the intranasal route, the toxic dose relationship is tetracaine 1, cocaine 5, benzocaine 10.4 and lidocaine 13.5. These comparisons indicate that benzocaine is far less toxic than the other compounds tested when administered via the intratracheal route. The data also indicate that when the intranasal route is used, benzocaine is far less toxic than tetracaine and cocaine but slightly more toxic than lidocaine.

Acute lethal dose studies using the oral and intraperitoneal routes in mice also indicate that benzocaine manifests a low degree of toxicity.

Studies of the effects of benzocaine on the cornea of rabbits to determine its potential for producing irritation were reviewed (Ref. 7). The concentrations used ranged from 4 to 20 percent in polyethylene glycol-4000 dilaureate. Benzocaine caused no detectable irritation of the eyes. The effect of benzocaine was compared with the effects of the hydrochlorides of dibucaine, tetracaine, and pramoxine. Dibucaine hydrochloride 2 percent and tetracaine hydrochloride 2 percent caused irritation consisting of a red, swollen conjuctival sac with copious mucous secretions surrounding the area. This condition persisted in these animals for 48 hours. Pramoxine hydrochloride 3 to 4 percent caused extreme swelling and inflammation at the experimental site. The irritation was accompanied by excessive mucous secretion. After 24 hours the corneal areas became blue in appearance, suggesting blindness.

The systemic effects of benzocaine absorbed percutaneously were studied. These studies were designed to assess the effects of benzocaine on the hematopoietic system and were conducted in rabbits (Ref. 7). Benzocaine 20 percent in a Carbowax™ base was applied to abraded rabbit skin after which blood samples were drawn from a marginal ear vein. Hemoglobin and methemoglobin levels were determined. In addition, erythrocyte, leukocyte, and differential counts were made. The hemoglobin level decreased to the same approximate levels in both the control and experimental animals. Methemoglobin levels increased to a maximum of less than 3 percent of the total hemoglobin. This response was essentially identical to that occurring in the control and experimental animals. Erythrocyte levels decreased in both the control and experimental animals while the leukocyte count was elevated in both the test and control animals. Differential counts revealed an increase in polymorphonuclear leukocytes and a decrease in lymphocytes in both the control and experimental groups. It was concluded, even though some minor change occurred in each of the parameters studied, that these changes were indistinguishable in the control and experimental groups and that these effects were apparently due to some phenomenon other than that of applying the ointment to the abraded skin.

The percutaneous safety of benzocaine was reported by Zaroslinski (Ref. 7) in a study investigating the topical effects of repeated application of benzocaine to the abraded skin. The experiment was designed to establish whether the use of benzocaine applied repeatedly to the abraded skin of rabbits caused any irritation or allergic response as well as systemic adverse effects. The study was conducted in eight female albino rabbits weighing 2.2 to 3.4 kilograms (kg). The back of each animal was closely clipped and then abraded in a specific area by repeatedly scraping the skin with the edges of a piece of wire screen, the teeth of which were 1 millimeter (mm) apart. The rabbits were divided into two groups. One group received 5 g ointment twice daily applied to the abraded surface. The second group served as a control and no ointment was applied. Blood samples were drawn from the marginal ear vein of each animal before and after abrading and tested for the hemoglobin-methemoglobin content, changes in erythrocytes, leukocyte counts, and differential counts. The areas of the abrasion were varied, that is, they were 3, 6, and 12 square inches, respectively. In all instances the quantity of ointment applied was constant, i.e., 5 g. The weighed amount of ointment was spread uniformly over the abraded areas. The skin was then manipulated by rubbing to cause absorption of the ointment. The entire trunk of each rabbit was protected by a light, muslin bandage. The drug was applied twice daily, 5 days weekly, over a period of 20 days. During this time 200 g of the ointment was applied to the abraded skin area of each of the rabbits. No observable local irritation or signs of allergic reaction was noted, nor were there any demonstrable systemic effects as judged by observations of the hematological parameters. During this period each test animal was inuncted with approximately 80 grams/kilogram (g/kg) ointment. The variations observed in the hemoglobin and methemglobin values were similar in both the control and the experimental animals.

Human safety data are available. Historically, the use of benzocaine preparations for topical anesthesia, both on the skin and mucous membranes, and for use internally has been reported many times and has been associated with a high degree of safety. It is beyond the scope of this Panel to cite in detail the case reports and other references pertaining to the clinical use of benzocaine, both as a prescription drug and in OTC preparations, since its introduction in 1903 by Einhorn. Many of these reports appear in the older medical literature and are not readily available or are reports of uncontrolled studies. The Panel, however, cautions

users that benzocaine therapy is not absolutely without hazard. In reviewing the literature on benzocaine, two types of adverse reactions have been noted. These reactions are either due to sensitization and are allergic in type, or result in the development of methemoglobinemia. The data cited in the medical literature on adverse reactions to benzocaine often focus on isolated cases or a small number of cases documenting adverse reactions. Many of these data are retrospective and involve the use of combinations which contain benzocaine as one of the ingredients. It is difficult to extrapolate from the frequency of occurrence of these isolated cases the probability of occurrence of adverse reactions in the general population, since no data are furnished on the frequency of application or the number of subjects treated with the drug.

As is the case with other drugs, benzocaine can act as a haptene and combine with proteins to cause a sensitivity mediated by IgE immune globulin type of antibodies. These antibodies act on mast cells, basophiles, and other cells in susceptible individuals and cause anaphylaxis, rhinitis, intrinsic asthma, urticaria, and atopic dermatitis. Benzocaine can also activate the thymus lymphoid system and cause topical sensitization of the cytotoxic type in the skin after repeated applications. The mechanism for development of sensitization is described elsewhere in this document. (See part II. paragraph G. above—Safety of External Analgesics.)

Fisher and associates (Ref. 8) studied the ability of para-phenylenediamine, a hair dye, to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. He found that in a group of 50 para-phenylenediamine-sensitive patients, 46 were still sensitive when tested three to ten years later. Of these 46, 11 were found to be also sensitive to benzocaine. They also found that of 24 patients sensitized to benzocaine, 10 were also sensitive to para-phenylenediamine. In a similar study, using a patch test, Gaul (Ref. 9) found that in a group of 580 dermatologic patients, 50 were sensitive to para-phenylenediamine and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, 3 were sensitive to benzocaine only and 3 were sensitive to para-phenylenediamine, procaine, and benzocaine. Patients showing sensitivity to a variety of substances were characterized as having cross-sensitivity, cross- and multiple sensitivity, and multiple sensitivity without cross-sensitivity. The Panel emphasizes that benzocaine is chemically dissimilar from para-phenylenediamine. Since benzocaine can act as a haptene and combine with a tissue protein to form strong covalent bonds to act as an allergen, these findings are not surprising to the Panel.

In the North American Dermatologic Study (Ref. 10), the incidence of benzocaine irritancy and sensitivity was less than 5 percent, equal to other commonly used drugs, and less than the more frequent sensitizers such as neomycin. These studies were performed on high risk allergic patients seeking treatment for dermatologic diseases. Benzocaine has often been referred to as a potent sensitizer and has been said to cause sensitization and cross-sensitization to other derivatives of amino-benzoic acid such as procaine, butamben, butethamine, tetracaine, and related compounds. The number of reported reactions has not been correlated with the total number of applications of the agent to individual subjects, with repeated applications, and with subjects who are not high risk (Ref. 11). Cross-sensitivity is defined as the capacity of an antibody to react not only with the substance responsible for the production but also with other antigens that are closely allied chemically. Mathieu, in reviewing the literature on cross-sensitivity, found few instances of cross-sensitivity among all the topical anesthetics (Ref. 12).

Prystowsky et al. did a prospective contact sensitivity study on 1,158 adult volunteers (Ref. 13). A pretest history of previous exposure to four allergens, including 5 percent benzocaine in petrolatum, was obtained before patch testing. The patch was removed at 48 hours and read at 5 days. The prevalence of positive reactions to 5 percent benzocaine was 0.17 percent. By history, 85 percent of the volunteers had been exposed to benzocaine. The investigators point out that 0.17 percent positive reactions in this study are in contrast to 1.6 percent positive reactions to benzocaine in a study of 127 patients referred to clinics for the evaluation of contact dermatitis. They concluded that "the results of this study indicate that contact dermatitis patient populations provide exaggerated estimates of the prevalence of sensitivity to contactants; figures in a general population are preferable in decision making concerning the safety of commercial products."

The Panel concludes that the available epidemiologic data on allergy, irritancy, and other reactions are inconclusive and in no way support the contention that benzocaine is a potent sensitizer. The number of adverse reactions are relatively few when one considers that benzocaine has been used since the early 1900's with wide marketing experience and very few complaints. It has been and is still one of the most widely used and safest topical anesthetics in OTC preparations (Refs. 7, 14, and 15). The Panel also believes that phrases such as "potent sensitizers," "common cross-sensitizers," and "highly allergic," etc. imply that these phenomena occur with greater frequency with benzocaine than with other drugs, and that such statements are unwarranted. The Panel finds little or no evidence of controlled, investigative, or epidemiological studies to support these contentions Calnan et al. (Ref. 16) evaluated sensitivity of various allergens by patch tests in 281 housewives exhibiting hand dermatitis in an effort to identify the offending allergen. Only 5 percent of these patients proved to be sensitive to benzocaine. However, substances occurring in household items or in chemicals such as balsams, nickel, and rubber were more common allergens than was benzocaine. Bandmann et al. (Ref. 17) in their reevaluation of some of the same data originally reported by Calnan et al. (Ref. 16) showed that the incidence of positive patch tests with benzocaine in male and female patients with allergic dermatitis was 3.3 percent and 4.5 percent. In view of the fact that only a fraction of the population exhibits any allergic dermatitis and that these tests were done on high risk populations, the Panel is of the opinion that the incidence of benzocaine sensitivity is quite low.

One death due to anaphylactic shock immediately following the administration of throat lozenges containing 10 mg benzocaine, 1 mg thyrothricin, and chlorophyll was reported by Hesch (Ref. 18). Circumstantial evidence cited by the author suggests that the death was drug related. However, it was impossible to state which of the components in the lozenge was the causative agent. The Panel is unaware of any similar cases of anaphylaxis that could be attributable to benzocaine or benzocaine-containing products applied to the skin, and concludes that even though benzocaine can act as a haptene and induce an IgE-mediated anaphylactic response, particularly on damaged skin, that the occurrence of anaphylaxis is extremely rare.

The use of 20 percent benzocaine ointment in 132 patients suffering from 22 types of dermatologic conditions was documented by White and Madura (Ref.

19). Included among these were 10 cases of infantile eczema, both dry and weeping, and 10 cases of varicose ulcers. Of the 132 cases, the relief obtained with benzocaine was inadequate in only two cases of atopic dermatitis and in two cases of lichen simplex chronicus. There were no cases of irritation or sensitivity reactions directly attributable to benzocaine. However, there were two cases of exacerbation of dermatitis veneata (poison ivy). Thus relief due to benzocaine was adequate to excellent in 126 out of 132 patients. The incidence of side effects was 2 out of 132 patients and these were not of a serious nature. This type of study in a population selected on the basis of dermatologic disease rather than on the basis of history of drug allergy tends to provide a better estimate of the incidence of sensitivity in the general population.

Adriani and Campbell (Ref. 20), in a study of the absorption of tetracaine applied on the mucous membranes in various areas of the body, comment that even though benzocaine was not included in this study, the systemic absorption of benzocaine is poor. It is to this lack of significant absorption that they attribute the absence of untoward reactions in 10,000 patients treated with 20 percent benzocaine ointment as a lubricant anesthetic for obtundation of pharyngeal and tracheal reflexes during introduction of tracheal catheters. Adriani and Zepernick (Ref. 21) reported a lack of adverse reactions in over 144,000 cases in which 20 percent benzocaine was used in hospitalized patients. The majority of these cases involved single applications for the lubrication of endotracheal tubes, oropharyngeal airways, and other instruments used in the pharynx and trachea during clinical anesthesia. These studies were performed at Charity Hospital, New Orleans. Since that time there has been a continuous use of benzocaine for the same purpose. It is estimated that the number of usages since their report was published is an additional 200,000, all without any adverse or allergic reaction.

Methemoglobinemia has been reported following the topical application of benzocaine on both the skin and the mucous membranes. However, this is an uncommon occurrence. It is alleged to occur in subjects less than 1 year of age (Reg. 3); however, it actually occurs at any age. Isolated reports of cases of methemoglobinemia, following the use of benzocaine-containing products have appeared in the literature since 1949.

Haggerty (Ref. 22) reported a case of a 1-month-old infant who became cyanotic after being treated for weeping diaper rash with an ointment containing 3 percent benzocaine, 1 percent methapyrilene hydrochloride, calamine, zinc oxide, and camphor. The diagnosis of methemoglobinemia was made by spectroscopic examination of the blood. The condition was reversed with methylene blue. Goluboff and MacFadyen (Ref. 23) reported one case of methemoglobinemia in a 3-month-old patient treated for severe eczema and pruritus with several products. One of these products contained salicylic acid, colloidal sulfur, and coal tar; another product contained one percent hydrocortisone in an ointment base; and one product contained 1.5 percent crude coal tar, 7.5 percent titanium dioxide, 7.5 percent zinc oxide, 2.5 percent calamine, 1 percent cetyltrimethyl ammonium bromide, and 5 percent benzocaine in a special water-soluble base. In addition the patient received intramuscular terramycin and oral elixir of phenobarbital. Treatment with methylene blue successfully reversed the methemoglobinemia. Determination of the causative agent was impossible due to the multiplicity of ingredients in the preparations.

Other isolated cases of a similar nature have been reported but the Panel believes that little would be added to understanding the nature of this reaction by reporting these additional cases in detail. Although the preponderance of reported cases of methemoglobinemia following topical use of benzocaine has occurred in infants, cases have been reported involving older children and adults. Bloch (Ref. 24) reported a case in a 6-year-old child and Bernstein (Ref. 25), in three adults. It has been suggested that the susceptibility in infants might be due to a deficiency of DPNH-dependent methemoglobin reductase, resulting in a diminished capacity to physiologically protect against methemoglobin-inducing foreign compounds. The experiences recorded by Bloch (Ref. 24) in a 6-year-old child suggest that a far less severe methemoglobinemia occurs in older children than in infants. The reactions in the three adults reported by Bernstein (Ref. 25) suggest that the reactions are mild. He found that definitive therapy was unnecessary. The methemoglobin imparts a bluish color (cyanosis) to the skin of white and lightly pigmented individuals. In black and heavily pigmented subjects, the cyanosis can be detected in the nailbeds or in the mucous membranes. The rapidity of development of the bluish color depends upon the rate and amount of benzocaine absorbed. In some cases it develops within 30 minutes to an hour after application.

Steinberg and Zepernick (Ref. 26) reported a case of methemoglobinemia during anesthesia which occurred in a 38-month-old black boy at the Charity Hospital in New Orleans. The boy had been anesthetized with cyclopropane on two previous occasions. On the first occasion, anesthesia was uneventful. On the second occasion, induction of anesthesia was followed by the development of cyanosis which was detected by observing the nailbeds. Anesthesia was discontinued and the operation was deferred until a week later. On the third occasion, anesthesia was induced in the usual manner with cyclopropane and the patient intubated. Cyanosis developed within 15 minutes and anesthesia was discontinued. He remained cyanotic even though he was awake and receiving 100 percent oxygen. There was no change in pulse o blood pressure. Within 4 hours he regained his normal color and had no apparent ill effects from the experience. A review of the anesthetic records revealed that anesthesia in the first instance, which was uneventful, was conducted by using an endotracheal tube that had been lubricated with petrolatum. On the second and third occasions the endotracheal tube had been lubricated with an ointment containing 20 percent benzocaine in propylene glycol. The child was studied further by Adraini and Zepernick (Ref. 27). Reapplication of 20 percent benzocaine to the mucous membranes o the mouth and on the tongue promptly produced cyanosis without the respiratory distress and the changes in pulse and blood pressure which would be anticipated if suboxygenation had been the causative factor. Blood drawn at this time was chocolate color. When analyzed spectroscopically, the absorption spectrum was characteristic of that produced by methemoglobin. Th cyanosis promptly disappeared after th intravenous administration of 1 mg/kg methylene blue in a 1-percent solution. On subsequent days various drugs wer applied to the mucous membranes and the blood was analyzed for methemoglobin. Since benzocaine is chemically allied to procaine, the latter being the diethylaminoethanol ester of aminobenzoic acid, procaine was applied to the mucous membranes and the blood analyzed for the presence of methemoglobin. None was found. A saturated aqueous solution of aminobenzoic acid was likewise applie on the mucous membranes with no

resultant cyanosis or evidence of methemoglobinemia. A paste consisting of propylene glycol and butamben was likewise applied without any development of methemoglobinemia. Since ethyl alcohol is used to esterify aminobenzoic acid to form benzocaine, it also was applied to determine whether there was cross-sensitization with the components of benzocaine. Alcohol, likewise, did not produce cyanosis nor did the blood show any increase in methemoglobin. Similarly, results using 1 percent lidocaine hydrochloride on the mucous membranes were negative. Propylene glycol applied to the mucous membranes likewise caused no methemoglobinemia. It appears obvious from these studies that the formation of the methemoglobin was due to the ethyl ester alone and that there was no cross-reactivity between aminobenzoic acid or any of its derivatives.

The majority of the reports the Panel has reviewed concerning the formation of methemoglobinemia following the use of benzocaine are single, solated cases or one, two, or three occurrences. It is difficult to extrapolate from these isolated cases the incidence of methemoglobinemia in the general population because the occurrences have not been in any way correlated with the total number of applications. Adriani and Zepernick (Ref. 21) reported no cases of sensitivity nor any other adverse reactions in over 144,000 cases after the use of a preparation containing 20 percent benzocaine for lubrication of endotracheal tubes and airways in hospitalized patients. Of these 144,000 cases, there was only one occurrence of methemoglobinemia following the application of the benzocaine ointment as a lubricant.

In a more recent survey performed by Adriani at Charity Hospital, it was found that 11,328 vials containing 20 percent benzocaine in propylene glycol were utilized from 1974 to 1977. It was estimated that 10 applications were made per vial. The total number of applications was estimated to be 116,360. The preparation was used by the anesthesia department for lubrication of airways and endotracheal tubes. During this period one 6-month-old infant devloped methemoglobinemia. This child was also receiving other drugs for the treatment of burns, presumably derivatives of sulfonic acid.

The action of benzocaine differs from drugs and chemicals such as acetanilid, sulfanilamide, the analine dyes, and the nitrites. Unlike benzocaine, these drugs and chemicals are oxidizing agents and cause methemoglobin to form at a more rapid rate than can be reduced by the enzyme, even though the reductase is present in adequate quantities in the red cell.

Methemoglobinemia is not life threatening, particularly when caused by the small amounts of benzocaine absorbed percutaneously or from the mucous membranes following a single application. Methemoglobin is also known as ferrihemoglobin and is incapable of carrying oxygen since the iron has been converted from the ferrous to the ferric state. There is an equilibrium between the concentration of ferrous and ferric components of iron in the hemoglobin. Normally, not more than 1 percent of the iron is in the ferric state. However, concentrations of methemoglobin up to 8 percent of the total hemoglobin can be present without cyanosis. Cyanosis becomes apparent when 10 to 15 percent of the total hemoglobin has been converted. Methemoglobinemia becomes symptomatic when 30 to 45 percent methemoglobin levels are attained if acutely induced. The symptioms are fatique, dyspnea, weakness, tachycardia, and headache, and are due to hypoxia produced by the lowered oxygen capacity of the blood.

There are at least three recogognized enzymatic processes which tend to keep the heme moiety of hemoglobin in the ferrous state and reduce the iron to the ferric state as rapidly as the ferrihemoglobin forms. The first mechanism employs an electron donor, nicotinamide adenine dinucleotide ($NAHDH_2$), which is formed from the oxidation of glucose and reduces the ferric heme to the ferrous state in the presence of the enzyme methemoglobin reductase. This pathway is the most important of the three and accounts for 67 percent of the conversion of the ferric iron to the ferrous state in red blood cells. The second pathway by which reduction of methemoglobin is accomplished involves the generation of nicotinamide adenine dinucleotide phosphate ($NADPH_2$), formed in a pentose pathway. In this reaction, methemoglobin can act as a cofactor that facilitates and accelerates the reaction. This pathway accounts for only 55 percent of the reduction of the iron in the red blood cells from the ferric to the ferrous state. The third mechanism involves a glutathione pathway. $NADPH_2$ in the presence of glutathione reductase (GR) reduces the oxidized glutathione to reduced glutathione The reduced glutathione in the presence of glutathione peroxidase is capable of destroying oxidant compounds capable of oxidizing hemoglobin. This pathway accounts for 12 percent of the methemoglobin converted to normal hemoglobin. Ascorbic acid is a reducing agent and can also be involved in the conversion. It reduces 16 percent of the methemoglobin; however, this is a nonenzymatic process.

The etiologic factors which alter equilibrium between ferrous and ferric iron can be classed into primary and secondary factors. Primary factors are hereditary. In the hereditary states, methemoglobinemia is due to a deficiency of $NAHDH_2$-dependent methemoglobin reductase and hereditary methemoglobinemia with an abnormal hemoglobin. These conditions are rare. The secondary factors are oxidant drugs.

Recently, Rao, Naraghi, and Adriani (Ref. 28) studied the blood levels of methemoglobin following the instillation of 1 g benzocaine in propylene glycol in the mouths of infants under 6 months of age and in adults. The methemoglobin levels in the controls ranged from 0.1 to 3.5 percent expressed in terms of diminution in oxygen-carrying capacity of the total hemoglobin. In infants there was an increase in the degree of unsaturation during the first hour to an average of 4.5. This is not as striking as one would anticipate. There was a gradual decrease in the methemoglobin content during the second hour, but it did not return to the pretreatment level in any subject until after the third hour. Surprisingly, the mean level in adults was higher than that found in infants. This is in direct opposition to what has been postulated concerning the ease of development of methemoglobinemia in infants following the use of the drug. The Panel concludes that the occurrence of methemoglobinemia following the use of benzocaine is rare. Normal infants and children are no more prone to its development than adults. Why this simple nonoxidizing chemical compound should cause this response on rare occasions is not known, but the Panel concludes it can be classified as an uncommon idiosyncratic response that is in no way injurious or life threatening.

(2) *Effectiveness.* There are studies documenting the effectiveness of benzocaine as an OTC external analgesic.

Benzocaine is an effective topical anesthetic on the skin and mucous membranes. There are many reports in the medical literature of its long, continued, and successful use as an analgesic, anesthetic, and antipruritic in the form of ointments, lotions, and dusting powders that attest to its efficacy (Refs. 3, 14, 21, and 29). These

studies, however, are subjective and uncontrolled. Benzocaine is not suitable for infiltration or perineural injection. When properly formulated with ingredients that insure its stability and continuous contact with a cutaneous or mucous surface, it provides prolonged analgesia or anesthesia (Ref. 14). When incorporated in a medium that is sufficiently alkaline to release bioactive quantities of the free base, it penetrates both the intact and the damaged skin (Ref. 14). Percutaneous absorption occurs, but the resulting blood levels are insignificant. Its pain relieving action is entirely within the skin or mucous membranes. The quantity circulating in the blood is insufficient to provide analgesia or anesthesia to parts of the body distal to the site of application or in the structures beneath the skin, such as the muscles, tendons, or joints. Although traces of benzocaine have been identified in muscles and tendons of rats, claims that the benzocaine present in muscles or joint tissues affords relief in areas other than the skin are regarded as Category II claims by the Panel.

The amount absorbed by the intact skin is insufficient to induce the subjective sensation of numbness even when 20 percent concentrations are used, however, enough is absorbed to elevate the pain threshold to produce analgesia. Numbness may be perceived when concentrated solutions in organic solvents or the crystals are applied to abraded skin surfaces, cuts, or open wounds. Aqueous solutions are too dilute to be effective. When solvents such as propylene or polyethylene glycol are used to formulate preparations, bioactive quantities are made available to the tissue fluids, and partial or complete blockade occurs relieving pain, burning, or itching. The ease with which benzocaine passes from an ointment or solvent is important. In vitro experiments performed by Ayres (Ref. 7) using cellophane membranes reveal that the rate of dialysis of benzocaine from an ointment varies with the type of ingredients used to prepare an ointment. These experiments indicate that the rate of dialysis of benzocaine is greater from water-soluble bases than from oleaginous bases or petrolatum. There is an increase in the quantity that dialyzes as the concentration of benzocaine is increased in the ointment. Although cellophane differs from skin and these results cannot be extrapolated to the penetration of benzocaine through human skin, they do suggest, and it can be inferred, that bioactive quantities pass into the skin more readily from water-soluble bases than from oleaginous bases.

Campbell and Adriani (Ref. 30) noted that topical anesthetics in oleaginous or petrolatum bases were not released as readily as they were from water-soluble bases and that blood levels were less and attained their peaks more slowly when the preparations studied were applied to mucous membranes. They were unable to detect the presence of topical anesthetics when these ointments were applied to first, second, and third degree burns produced experimentally in dogs. Since the introduction of newer and more suitable solvents, such as the glycols, there has been a renewed interest in the use of benzocaine as a topical analgesic because of greater efficacy of preparations formulated with these solvents compared to the oleaginous bases and dusting powders used previously. The concentration of bioactive benzocaine in the tissue fluids is insufficient to penetrate large nerve trunks. The effect of benzocaine is entirely at the terminal pain receptors in the skin.

Techniques for performing controlled studies to determine the efficacy of topical anesthetics on the intact normal skin and the intact damaged skin have not been satisfactory. There is a paucity of data to support claims of efficacy on the skin from controlled studies. Misconceptions are still prevalent regarding percutaneous absorption of drugs. The belief that most drugs are not readily absorbed through the skin is widespread. Data on percutaneous absorption of benzocaine have been obtained from uncontrolled studies and have not been substantiated by controlled studies.

Recently, Adriani and Dalili (Ref. 29) devised a method for stimulating the pain receptors in the skin using an electric current and producing the sensation of itch. That permitted them to perform controlled studies of topical anesthetics applied to the intact skin. They used an alternating pulsatile current delivered from a Grass SS–44 model stimulator which selectively activates the receptors for itch. The current that was used consisted of impulses of sine waves of 30 cycles per second of 5 milliseconds duration, with a 2-millisecond delay. Repeated stimulation produced the sensation of itch and burning without injury to the dermal structures. A subminimal stimulus excites the pain receptors and they respond with the sensation of itch. A further increase in the intensity of the current converts the sensation of itch to one of pain. From 25 to 40 volts were necessary to deliver the required current. The necessary amperage varied from subject to subject. The volar surface of the forearm was used as the test site. An indifferent electrode was fixed to the dorsum of the forearm over guaze soaked with saline. A pinpoint metal tip was used as the exploring electrode. Controlled values were established at multiple points over the test sites. A film of the preparation to be evaluated was applied over a given area and allowed to remain for 30 minutes. Areas 1 x 1 centimeter (cm) were then wiped dry at 5-minute intervals and stimulated at 1- to 2-second intervals until itching was perceived. Generally, 1 hour elaspsed before the entire area was wiped and tested. A single application of the preparation to be tested for 30 to 60 minutes established whether the preparation was clinically useful.

The study was conducted on 150 volunteers. Each preparation was tested in six randomly selected subjects. The number was increased until a definite rating could be established when responses were not uniform in all six subjects. These authors felt that a preparation requiring more than 30 minutes to establish its analgesic effects was not clinically useful. The identities of the preparation were known to the evaluators but not to the subjects. Comparisons were made with placebos. The responses to electrical stimulation were graded as 0 when the response to stimulation was not obtunded, 1+ when the block to the electrical stimulation was partial (increasing the current reproduced the sensation of itch), and 2+ when no sensation of itching, pricking, or burning resulted from the electrical stimulation even when the intensity of the current was increased. These workers found that benzocaine base 5 to 20 percent caused a partial to complete blockade of the receptors to the sensation of itch or burning. The duration of analgesia ranged from 4 to 6 hours if the film of the ointment or solution remained undisturbed. These authors found that benzocaine was not effective in less than 5 percent concentration. The blockade was not complete at 5 percent because increasing the intensity of the current caused the receptors to respond. This ability to respond decreased in intensity as the concentration of benzocaine was increased from 5 to 20 percent (Ref. 16).

The effects of the salts and bases of individual topical anesthetics in obtunding itching and burning of pathologic origin induced by first degree burns was also determined (Ref. 16). The burns were produced on the volar aspects of the forearm with ultraviolet

light from a GE Model F Type 2 lamp held 50 cm from the skin for 2 to 3 minutes. The burns caused an erythema in 90 percent of the subjects 2 to 3 hours after exposure to the ultraviolet light. The subjects not only complained of itching and burning but also commented that the erythematous areas were hypersensitive to touch and pressure. As soon as the subjects complained of symptoms, benzocaine was applied to the burns in concentrations ranging from 1 to 20 percent. Relief was obtained for periods of 4 to 6 hours with concentrations of 5 to 20 percent benzocaine in propylene glycol. The preparation was allowed to remain in contact with the skin for 30 minutes before the areas were tested by electrical stimulation. While the subjects treated with benzocaine in concentrations of 5 percent of more did not respond to the electrical stimulation, those with placebos did. Subjective manifestations were graded according to what the patient said concerning the pain. That both cold and touch could still be perceived after application of a preparation was assumed by these authors to be confirmatory evidence that the drug does not block all the sensory nerve receptors in the subepidermal areas and that receptors are still active after the burn. They added hydrochloric and lactic acids to 20 percent benzocaine in propylene glycol. Acidification completely nullified the activity of the benzocaine. Their study clearly demonstrates that the basic form of benzocaine is bioactive and penetrates the intact normal and the intact damaged skin and obtunds the sensation of pain, burning, and itch. One phase of their study involved the testing and comparison of 30 commercially available OTC topical anesthetics, sprays, creams, and ointments promoted as topical analgesic, anesthetics, and antipruritics. The data from this phase of the study are quite revealing. Among the 10 benzocaine-containing preparations, only one was effective—this consisted of 20 percent benzocaine base in propylene glycol.

These authors concluded that the lack of efficacy of the manufactured preparations, all of which were combinations or contained the salt form of the topical anesthetic, may be due to one or a combination of the following factors: (i) The preparations contain insufficient active ingredient. All 10 preparations contained less than 5 percent benzocaine except the one which was effective.

(ii) The bases of the topical anesthetics, being less stable than the salts, may have undergone chemical change. Benzocaine, however, is more stable than the soluble "caine" bases.

(iii) Nonanesthetic ingredients present in a mixture nullify the action of the local anesthetic.

(iv) The anesthetic was retained by the solvent so that a bioactive quantity was not delivered to the receptors in the skin.

(v) Ingredients in the preparation may have augmented the cutaneous barrier effect and decreased penetration.

(vi) The burn caused by the ultraviolet light altered the epithelial barrier and decreased penetrability of the active ingredients.

Thus the Panel concludes that benzocaine when properly formulated is an effective and safe topical analgesic, anesthetic, and antipruritic on the intact or damage skin.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 5 to 20 percent concentration of benzocaine to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(2) Adriani, J., "Local Anesthetics," *in* "The Pharmacology of Anesthetic Drugs," 5th Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 131–145, 1970.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 269, 1977.

(4) Letter solicited by John Adriani, M.D. from Dr. A. Shansky, in OTC Volume 060150.

(5) OTC Volume 060118.

(6) Astrom, A. and N. H. Persson, "The Toxicity of Some Local Anesthetics After Application on Different Mucous Membranes and Its Relation to Anesthetic Action on the Nasal Mucosa of the Rabbit," *Journal of Pharmacology and Experimental Therapeutics,* 132:87–90, 1961.

(7) OTC Volume 060073.

(8) Fisher, A. A., A. Pelzig, and N. B. Kanof, "The Persistence of Allergic Eczematous Sensitivity and the Cross-Sensitivity Pattern to Paraphenylenediamine," *Journal of Investigative Dermatology,* 30:9–12, 1958.

(9) Gaul, L. E., "Types of Sensitization Disclosed by Positive Patch Testing to Paraphenylenediamine and Benzocaine," *Annals of Allergy,* 18:738–745, 1960.

(10) North American Contact Dermatitis Group, "Epidemiology of Contact Dermatitis in North America 1972," *Archives of Dermatology,* 108:537–540, 1973.

(11) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(12) Mathieu, A., "Allergic Reactions to General and Local Anesthetics," *in* "Handbook of Refresher Courses—220," American Society of Anesthesiologists, Park Ridge, IL, pp. 1–5, 1975.

(13) Prystowsky, S. D. et al., "Contact Sensitivity to Nickel, Neomycin, Ethylenediamine, and Benzocaine in a General Population: Relationships Between Age, Sex, History of Exposure, and Reactivity to Standard Patch Tests," *American Federation for Clinical Research,* (Abstract) Meeting, April 18 to May 1, 1978.

(14) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(15) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 186–197, 1973.

(16) Calnan, C. D., H. J. Bandmann, E. Cronin, S. Fregert, N. Hjorth, B. Magnusson, K. Malten, C. L. Meneghini, V. Pirila, and D. S. Wilkinson, "Hand Dermatitis in Housewives," *British Journal of Dermatology,* 82:543–548, 1970.

(17) Bandmann, H., C. D. Calnan, E. Cronin, S. Fregert, N. Hjorth, B. Magnusson, H. Maibach, K. Malten, C. Meneghini, V. Pirila, and D. Wilkinson "Dermatitis from Applied Medicaments," *Archives of Dermatology,* 106:335–337, 1972.

(18) Hesch, D. J., "Anaphylactic Death from the Use of a Throat Lozenge," *The Journal of the American Medical Association,* 172:12–15, 1960.

(19) White, C. J. and J. W. Madura, "Topical Anesthesia in Dermatology," *Post Graduate Medicine,* pp. 519–520, 1951.

(20) Adriani, J. and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:527–530, 1956.

(21) Adriani, J. and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association,* 188:711–716, 1964.

(22) Haggerty, R. J., "Blue Baby Due to Methemoglobinemia," *The New England Journal of Medicine,* 267:1303, 1962.

(23) Goluboff, N. and D. J. MacFayden, "Methemoglobinemia in an Infant," *Journal of Pediatrics,* 47:222–226, 1955.

(24) Bloch, A., "More on Infantile Methemoglobinemia due to Benzocaine Suppository," *Journal of Pediatrics,* 67:509–510, 1965.

(25) Bernstein, B. M., "Cyanosis Following the Use of Anesthesin (Ethyl Aminobenzoate)," *Review of Gastroenterology,* 19:411–412, 1952.

(26) Steinberg, J. B. and R. G. Zepernick, "Methemoglobinemia During Anesthesia," *Journal of Pediatrics,* 61:885–886, 1962.

(27) Adriani, J. and R. Zepernick, "Summary of Methemoglobinemia: Study of Child Receiving Benzocaine." Letter to the Commissioner in OTC Volume 060150.

(28) Rao, V. K., M. Naraghi, and J. Adriani, "Methemoglobinemia Following the Use of

Topical Local Anestetics," Draft of unpublished paper, in OTC Volume 060150.

(29) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia*, 50:834–841, 1971.

(30) Campbell, D. and J. Adriani, "Absorption of Local Anesthetics," *Journal of the American Medical Association*, 168:873–877, 1958.

d. *Benzyl alcohol.* The Panel concludes that benzyl alcohol is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Benzyl alcohol is one of the alcoholic or hydroxy type topical anesthetics. Benzyl alcohol is phenyl methanol. It may also be looked upon as methyl alcohol with a phenyl group replacing one of its hydrogen atoms. It is also known as phenmethylol hydroxy toluene. It is found in nature in a free state in oil of jasmine (6 percent) and in the form of esters in Peru balsam, tolu balsam, and storax. The commercial product is synthetic and made by hydrolyzing benzyl chloride or by reducing benzaldehyde. Benzyl alcohol is a colorless liquid with a faint aromatic odor. It has a sharp burning taste. It boils at 206° C. It has a specific gravity of 1.042 to 1.047. One g dissolves in approximately 30 g water, making solutions of approximately 4 percent concentration. Aqueous solutions are neutral. Solutions may be sterilized by boiling. Benzyl alcohol is soluble in alcohol (1 g in 1.5 mL). It is miscible with alcohol, ether, and chloroform. It dissolves in vegetable oils. Oxidation coverts it to benzaldehyde. Slow oxidation occurs if it is exposed to the air for days or weeks. It is stable in stoppered containers (Refs. 1 and 2).

(1) *Safety.* Clinical use has confirmed that benzyl alcohol is safe in the dosage range used in an OTC external analgesic.

Benzyl alcohol is relatively nontoxic. It has been used orally as an antispasmodic agent and rectally as a topical anesthetic. It has been used rectally in combination with paraldehyde to anesthetize the mucosa and prevent explusion of the drug (Refs. 2 and 3). It is converted to hippuric acid in the body and this metabolite is excreted into the urine (Ref. 2). The effect of large doses was studied in animals by Macht (Ref. 4). The minimum lethal dose of pure benzyl alcohol in white mice is 1 mL/kg. The minimum lethal dose in rats ranges from 1 to 3 mL/kg. In dogs, 2 mL/kg of benzyl alcohol injected intravenously, peritoneally, subcutaneously, and intramuscularly were never fatal. Convulsions and cardiac depression, characteristic of the "caine" type of topical anesthetics, have not occurred when therapeutic or toxic doses of benzyl alcohol have been administered to man or animals. Lethal doses in mice cause respiratory failure and in some cases, convulsions. Larger animals, such as dogs, do not manifest these responses. Although benzyl alcohol can, like any other drug, act as a haptene and be antigenic, cases of sensitization have not come to the Panel's attention. The potential for sensitization is lower than it is with the "caine" type of topical anesthetics (Ref. 5).

(2) *Effectiveness.* There are studies documenting the effectiveness of benzyl alcohol as an OTC external analgesic.

Benzyl alcohol belongs to the hydroxy group of topical anesthetics and differs in chemical behavior from the "caine" type drugs. Benzyl alcohol is lipophilic and penetrates the intact or damaged skin. Aqueous solutions of benzyl alcohol are neutral. It does not form salts. Benzyl alcohol is not ionized and penetration into the skin and pharmacologic activity do not depend upon pH. It temporarily relieves itching and burning of painful cutaneous lesions when it is applied topically (Refs. 5, 6, and 7).

Macht (Ref. 4) studied the topical anesthetic effects of benzyl alcohol. He obtained anesthesia by applying aqueous solutions to the mucous membranes of the mouth, tongue, gums, and lips of human beings. The pure alcohol produces a stinging effect when applied to the tongue, followed by a sensation of numbness which may last as long as 2 hours. Macht was able to obtain anesthesia of the skin by direct application of the pure alcohol. Solutions of 1 percent (aqueous) produced corneal anesthesia in rabbits. Solutions of benzyl alcohol produce sensory and motor blockade when they are applied to isolated nerves of frogs. Macht (Ref. 4) obtained both motor and sensory blockade by applying 1 percent solutions of benzyl alcohol to isolated sciatic nerves of dogs. Benzyl alcohol has been used for infiltration and perineural block. Stronger solutions are locally irritating and may cause tissue damage.

Benzyl alcohol manifests varying degrees of bacteriostatic and antiseptic activity. However, this effect does not apply to all pathogenic bacteria, and reliance cannot be placed upon it. Benzyl alcohol is effective topically on the skin to relieve itching and other discomfort due to cuts, insect bites, or abrasions. Solutions composed of equa parts (33 percent) of benzyl alcohol, water, and ethyl alcohol are effective i relieving itching and burning on the sk (Ref. 2). Ointments consisting of 10 percent benzyl alcohol in large doses have been used for topical application the skin.

The duration of action of benzyl alcohol in the usual therapeutic doses i brief and depends upon the area of application. The latent period on the mucous membranes is approximately 2 minutes. The duration of action is usually less than 30 minutes. The duration of analgesic action on the skir is variable, usually depending upon the surface to which it is applied (Refs. 2 and 8). The effect is sustained if ointments or lotions that permit continuous contact are used.

The pure alcohol causes smarting an burning initially when it is applied to t skin. Although benzyl alcohol is effective as a topical anesthetic, Adria and Zepernick (Ref. 8) found its efficac to be less than that of the "caine" type drugs. However, the Panel concludes that benzyl alcohol is safe and effectiv for use on the intact or damaged skin i the dosage range used as an OTC external analgesic.

(3) *Dosage—For adults and children years of age and older:* Apply a 10 to 33 percent concentration of benzyl alcoho to effected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosag except under the advice and supervisio of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic and antipruritic active ingredients. (see part III. paragraph B.1. below—Categor I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway NJ, p. 148, 1976.

(2) Osol, A. and R. Pratt, "The Dispensato of the United States," 27th Ed., J. B., Lippincott Co., Philadelphia, PA, p. 190, 1973

(3) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner*, 25:82–86, 1962.

(4) Macht, D. V., "A Pharmacological and Therapeutic Study of Benzyl Alcohol as a Local Anesthetic," *Pharmacy and Experimental Therapeutics*, 11:263–279, 1918

(5) Adriani, J., "Local Anesthetics," *in* "Th Pharmacology of Anesthetic Drugs," 5th Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 131–145, 1960.

(6) Barnes, M. E., "Death Following the Administration of Thymol," *Journal of the American Medical Association*, 79:964–965, 1922.

(7) Sollmann, T., "A Manual of Pharmacology and Its Application to

Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, PA, p. 340, 1957.

(8) Adriani, J. and R. G. Zepernick, "Comparative Potency and Duration of Action of Topical Anesthetic Drugs in Man," *Anethesiology*, 24:120, 1963.

e. *Butamben picrate.* The Panel concludes that butamben picrate is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Butamben is the butyl ester of *p*-aminobenzoic acid. It is made by esterifying *p*-aminobenzoic acid with butyl alcohol. Butamben is a primary amine and is therefore a base. Butamben is a white, crystalline, tasteless, and odorless powder that melts at between 57° to 59° C. When boiled with acids it is slowly hydrolized to the alcohol and acid. It is similar in its pharmacologic actions to benzocaine (Refs. 1 and 2). Butamben has also been called butesin, butaform, plantoform, and sturoform. Butamben belongs to the group of topical anesthetics classified as the insoluble topical anesthetics (Ref. 1).

As with benzocaine, butamben has a low degree of water solubility. One g dissolves in 7 liters of water. It is soluble in the glycols, dilute solutions of acids, chloroform, ether, and fatty oils. Like other nitrogenous bases, butamben forms salts and esters with acids. Butamben unites with two molecules of picric acid (trinitrophenol) to form a yellow complex, butamben picrate. Both butamben base and butamben picrate are topical anesthetics acting primarily at terminal nerve endings and not on the nerve trunks (Refs. 2 and 3). Both products were introduced in 1926 at approximately the same time.

Butamben picrate is an odorless powder with a bitter taste. It melts at between 109° to 110° C. One g dissolves in 2 liters of water. It is soluble in fatty oils and oleaginous bases. The powder is yellow and is incorporated into ointments for topical application. Butamben picrate slowly releases butamben and picric acid when in contact with moisture. The picric acid stains the skin and other objects. As is the case with salts of topical anesthetics, the butamben picrate complex does not penetrate the intact skin, but will be absorbed when the stratum corneum has been disrupted or the epithelial barriers are destroyed (Refs. 1 and 4).

(1) *Safety.* Clinical use has confirmed that butamben picrate is safe in the dosage range used as an OTC external analgesic.

Due to the ingredient's low water solubility and poor absorbability, systemic toxicity which may occur with the local anesthetics of the "caine" type is not observed with butamben. The base penetrates the intact skin where it exerts its blocking action on the nerve endings of pain receptors. Due to its poor solubility in water, quantities absorbed from the skin that pass into the blood are relatively minute. Plasma levels that cause cardiac depression and central nervous stimulation characteristic of the "caine" type of topical anesthetics are virtually unknown. The toxic dose for animals is high. By the intraperitoneal route, 1,000 mg/kg butamben picrate killed 2 of 3 mice while 1,500 mg/kg killed 3 of 3 animals (Ref. 5). When administered orally to mice, 2,000 mg/kg caused no deaths in 3 of 3 mice. The mice were observed for 72 hours.

The oral toxic dose for man is not known. Due to the ingredient's poor water solubility and the lack of reports on systemic toxicity, the Panel feels justified in assuming that the toxicity of butamben is extremely low. The Panel also emphasizes that the animal toxicity cited above may be due to the picric acid and not the free base. Irritancy of butamben picrate is low due to the solubility characteristics. The sensitizing and irritancy potential of butamben appears to be low. Reports of irritancy by the base have not been submitted to the Panel, and standard textbooks and other pertinent medical literature do not mention reactions due to sensitization or irritation. Such terms as "potent sensitizer" and "frequent sensitizer," which have been used to characterize cutaneous reactions from the use of benzocaine, are not applied to butamben. Sensitization has been reported following the use of butamben picrate (Ref. 6). This aspect of adverse reactions due to this salt is discussed below. Although the Panel states that butamben has a low potential for sensitization, it emphasizes that butamben is not totally without hazard and can, like benzocaine and other drugs, be antigenic and cause anaphylaxis and other types of allergic reactions. Toxic systemic reactions, with the exception of sensitization, have not occurred (Ref. 7).

The Panel concludes that any adverse effects occurring from butamben picrate are due to the picric acid that is released and not to the butamben. Saturated aqueous solutions of picric acid have been used externally in burn dressings. Alcoholic solutions of picric acid are irritating. The picric acid is readily absorbed and causes systemic toxicity. Locally, the handling of the dry powder of picric acid produces an eczematous dermatitis ("picric itch"). Systemically toxic doses destroy red blood cells and cause gastroenteritis, nephritis, and hepatitis. The tissues are stained yellow. A part of the absorbed picric acid is excreted unchanged and some is converted to picramic acid by the liver and excreted into the urine (Refs. 8 and 9).

Butamben picrate has not produced irritation, but cases of sensitization have been reported in approximately 1 of 6,000 cases in which it was used. It can be stated from available data that sensitization is not infrequent. Patch or contact tests should be done cautiously because generalized reactions may follow in susceptible individuals. Whether the dermatitis that has occurred is due to the butamben or to the picric acid is not established, but the Panel believes, from evidence submitted and past experiences with picric acid used alone for burns, that picric acid is the offender.

(2) *Effectiveness.* There are studies documenting the effectiveness of butamben picrate as an OTC external analgesic.

The analgesic effects of butamben picrate are due to the release of butamben, which possesses a topical anesthetic effect and whose pharmacologic effects closely resemble those of benzocaine. When applied to the mucous membranes, butamben in concentrations of 1 to 12 percent in propylene glycol provides topical anesthesia.

Butamben in the form of the base is effective as a topical analgesic, anesthetic, and antipruritic on the intact and damaged skin (Refs. 10 and 11). The pharmacologic and topical analgesic action of the base are due to its lipophilic action. It is absorbed in minute quantities through the skin. Data on its metabolic fate in the body are not available. Because it is an ester of aminobenzoic acid and most aminobenzoic acid ester topical anesthetics are hydrolyzed by the pseudocholinesterases in the body, the Panel regards hydrolysis by the esterases as a possible metabolic pathway. It exerts its analgesic effect superficially in the skin. It does not penetrate in sufficient quantities to exert any beneficial effect on structures beneath the skin or systemically (Ref. 7).

Butamben reacts with acid to form salts which are ionized and do not readily penetrate epithelial barriers. The picrate is effective on damaged skin but not effective on the intact skin. Butamben is less potent and effective than benzocaine. It has a longer latent

period and a shorter duration of action than benzocaine, probably due to its poor water solubility (benzocaine is approximately 2½ times more soluble in water than butamben). The powder is effective if dusted on abraded skin and other open cutaneous lesions.

Butamben picrate is effective on the skin for the temporary relief of pain due to cutaneous lesions in which the skin is damaged and the drug has ready access to the terminal pain receptors. Adriani and Dalili (Ref. 12) found that 1 percent butamben picrate did not obtund the sensation of pain and itch elicited by electrical stimulation of the intact skin. They likewise noted that when butamben picrate was applied to intact erythematous skin burned with ultraviolet light, it did not relieve the discomfort due to the burn. Likewise, the receptors for pain and itch in the burned areas continued to respond to electrical stimulation, indicating that butamben picrate had not penetrated the intact skin and blocked these receptors.

An aqueous solution of 1:2,000 of the picrate is anesthetic to the conjunctiva and cornea and has been used in the eye. However, regardless of the vehicle, picrate is not used or recommended for this purpose for OTC use.

Butamben picrate is an analgesic, anesthetic, and antipruritic agent and can be used for all Category I indications. However, it has been recommended particularly for burns. The claim is made that it combines the anesthetic property of butamben and the antiseptic properties of trinitrophenol (Ref. 5). Picric acid has a phenol coefficient of 4.5. The value of picric acid in the treatment of burns was described by a French medical student in 1896 (Ref. 5). Butamben picrate allegedly leaves the surfaces of the burn flexible and pliable (Ref. 5). Presumably, it acts by coagulating proteins. Butamben picrate possesses some antimicrobial activity, believed to be due to the released picric acid. The current labeling on a product containing butamben picrate ascribes its antimicrobial action to nitromersol which is added to the finished product, but the submission for this product, evaluated by the Panel, ascribes this effect to picric acid (Ref. 5). The Panel concludes that the use of picric acid for treatment of burns is obsolete. Picric acid is not an analgesic and contributes no part to the relief of pain or itching obtained by applying the picrate to cutaneous lesions.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 percent concentration of butamben picrate to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:*

(i) "Do not use over extensive areas of the body."

(ii) "This product stains the skin and tissues, clothing, and other objects yellow."

References

(1) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 192–193, 1976.

(3) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(4) Adriani, J. and R. G. Zepernick, "Comparative Potency and Duration of Action of Topical Anesthetic Drugs in Man," *Anesthesiology,* 24:120–121, 1963.

(5) OTC Volume 060039.

(6) Lane, C. G. and R. Luikart, "Dermatitis from Local Anesthetics with a Review of One Hundred and Seven Cases from the Literature," *Journal of the American Medical Association,* 14:717–720, 1951.

(7) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(8) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics, 5th Ed., Macmillan Publishing Co., Inc., New York, p. 391, 1975.

(9) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 340, 1957.

(10) Adriani, J., R. Zepernick, J. Arens, and E. Anthement, "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

(11) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(12) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

f. *Camphor.* The Panel concludes that camphor is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient, at a concentration of 0.1 to 3.0 percent, depresses cutaneous receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below. In concentrations higher than 3 percent, but not exceeding 11 percent, camphor stimulates cutaneous receptors and should bear the labeling for topical counterirritants set forth below (Refs. 1 and 2).

Camphor is a member of a cyclic group of hydroaromatic substances known as terpenes (Refs. 1, 3, and 4). Camphor is 2-bornanone, a 2-ketone of heptane which occurs in nature in the camphor tree *(Cinnamum camphora),* an evergreen native to eastern Asia. Natural camphor is obtained from all parts of the camphor tree. Camphor is also made synthetically from alpha-pinene, a constituent of turpentine. Approximately three-fourths of the camphor used is prepared synthetically. Natural camphor is dextrorotatory, while the synthetic preparation is racemic and optically inactive. Both forms are pharmacologically active. Camphor melts at 179.75° C at atmospheric pressure. It sublimes readily. At 25° C, 1 g dissolves in 800 mL water, 1 mL ether, 1 mL alcohol, 0.5 mL chloroform, 0.4 mL acetone, and 1.5 mL oil of turpentine. Camphor, because it is a ketone, is converted by reduction to borneol, a secondary alcohol. Camphor has a peculiar tenacity and cannot be powdered in a mortar until it is moistended with an organic solvent. It liquefies when triturated with menthol, thymol, phenol, and resorcinol. It is not compatible with oxidants such as potassium permanganate. Camphor forms complexes with cresol (camphor metacresol) from which both ingredients can be released. Camphor is freely miscible with volatile and fixed oils. When applied to the skin, camphor produces a feeling of warmth and a mild local anenthetic action that may be followed by numbness (Refs. 1 and 3).

Several camphor products are described in the official compendia. Camphor liniment, National Formulary X, contains 20 percent camphor in cottonseed oil. This preparation is commonly called "camphorated oil." Other topical products containing camphor are camphor and soap liniment, United States Pharmacopeia XIII (4.5 percent camphor); camphor spirit, National Formulary X (10 percent camphor); and camphor ointment, National Formulary IX (20 percent camphor) (Ref. 5).

(1) *Safety.* Clinical use has confirmed that camphor is safe in the dosage range used as an OTC external analgesic.

Camphor is metabolized if ingested orally or assimilated by other routes. Camphor is first oxidized by the liver to campherol and the campherol is then conjugated with glucuronic acid by the liver. The conjugate is excreted into the

urine. Camphor is absorbed from the mucous membranes and at the mucocutaneous junctions. Camphor is absorbed if injected subcutaneously. It is also absorbed from the intact and damaged skin because it is nonionized and lipophilic. Excessive doses may be fatal (Ref. 1).

The minimal lethal dose for rabbits is 2 g/kg. The median lethal dose subcutaneously for rats is 2.2 g/kg. The oral median lethal dose for guinea pigs is 180 mg/kg. In mice, the LD_{50} is 30 mg/100 g when administered intraperitoneally. The estimated minimal lethal dose for man is 2 g when ingested orally. One adult survived ingestion of 1.5 g camphor. Ingesting 0.7 to 1.0 g camphorated oil proved fatal to a child (Ref. 6). Accidental poisoning has occurred from ingesting the oil when it has erroneously been administered for castor oil. Cases continue to the reported. The Panel considered various comments, reports, and editorials submitted to it concerning the toxicity and frequency of poisonings from camphor-containing preparations, particularly in children. The Panel has taken cognizance of these cases of poisoning and those that continue to occur. However, the Panel is unaware of any case of poisoning that has occurred from topical administration despite the fact that camphor, due to its lipophilic nature, is know to penetrate the skin. The Panel is also aware of its use as a component of paregoric (camphorated tincture of opium) which is widely used as an antidiarrheal in adults and children and as a sedative and analgesic in infants and children. The Panel, therefore, considers camphor to be safe for topical use. Camphor in oil was once used parenterally as an analgesic. Systemically, camphor stimulates the central nervous system. Excessive doses produce convulsions which may be fatal. But cases of systemic poisoning from topical application have not been reported. Camphor is not a common skin sensitizer but can, in concentrations above 3 percent, be an irritant. It is used as a counterirritant in topical antirheumatic preparations (Ref. 2).

Of the submissions to the Panel, 12 with claims of counterirritancy contain camphor. In reviewing these submissions, the Panel observed that in no instance was camphor the sole, or even the principal irritant in the formula. Only 1 of these 12 products had a camphor content greater than 6 percent. Eleven of the products had a camphor content ranging from approximately 1 to 6 percent. The average camphor content was approximately 4 percent (Refs. 7 through 16).

Topical camphor products of the counterirritant type have an excellent safety record. Marketing figures from 1972 indicate that 6 counterirritant products containing camphor accounted for 12,000,000 or more sales. Customer compliants were no greater than 1:1,000,000 (Refs. 8 through 10 and 12 through 14).

As previously indicated, the Panel does not consider concentrations of 20 percent camphor poisonous or harmful for topical use. However, the Panel has been unable to find any acceptable reasons for the continued employment of camphor alone as a topical counterirritant at this concentration. In present self-medication practices, the Panel concludes that a maximum camphor content of 11 percent is appropriate and probably no less effective a counterirritant than are higher concentrations. The concurrent use of other irritants, and advances in vehicle formulations support this conclusion. The Panel recommends 11 percent as the maximum concentration of camphor that may be marketed, with appropriate label warnings, in OTC counterirritant self-medication products.

(2) *Effectiveness.* There are studies documenting the effectiveness of camphor as an OTC external analgesic. Due to the wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that camphor is effective for use as an OTC external analgesic.

The Panel has evaluated the topical use of camphor as an analgesic, anesthetic, and antipruritic, and as a counterirritant. In concentration of 3 percent or less by weight, camphor is an effective antipruritic and relieves the discomfort due to skin lesions characterized by itching and burning on the skin at the site of application. It is believed to act upon sensory receptors in the skin in the same manner as the hydroxy or alcohol types of topical anesthetics. In concentrations exceeding 3 percent, particularly when combined with other ingredients that produce conterirritation, camphor stimulates the nerve endings in the skin and induces relief of pain and discomfort in muscle joints and other subcutaneous structures at a site distal to its application on the integument. The counterirritant effects and dosage forms are described below. The Panel emphasizes that two distinct and dissimilar mechanisms are involved in the effectiveness of camphor as a topical analgesic. By one mechanism, the activity of the pain receptors in the skin is obtunded, and by the second mechanism, the receptors inducing pain and other stimuli are stimulated and act by counterirritation (Refs. 1 and 2). Numerous clinical reports regarding the ability of camphor to relieve itch are available (Refs. 1, 2, and 17). Controlled double-blind studies are not available.

Camphor most likely exerts its antipruritic effects in a manner similar to those exerted by the hydroxy or alcohol type of compounds. When applied to the skin it produces a sense of warmth followed by a sensation of numbness. Topically, camphor is weakly antiseptic, but this attribute is of no practical significance as far as effective antimicrobial activity is concerned. In addition to camphor's use as an antipruritic, the Panel evaluated it as a counterirritant. After careful consideration of the irritant characteristics of camphor and the various formulations in which it is currently used, the Panel concludes that camphor is an effective counterirritant (Refs. 7, 8, 9, 11, 12, 14, and 15). The odor of camphor may play a role in the relief of pain (Refs. 1, 2, and 17). The psychological component of the effect of drugs in causing pain relief by their placebo effect cannot be ignored.

(3) *Dosage*—(i) *For use as a topical analgesic, anesthetic, and antipruritic: For adults and children 2 years of age and older:* Apply a 0.1 to 3.0 percent concentration of camphor to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For use as a topical counterirritant: For adults and children 2 years of age and older:* Apply a 3 to 11 percent concentration of camphor to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* Based upon the dosage, the Panel recommends the applicable Category I labeling for products containing topical analgesic, anesthetic, antipruritic, or counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 220, 1973.

(2) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes." *in* "The Pharamacological Basis of Therapeutics," 4th Ed., Edited by

Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 993, 1970.
(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 219, 1976.
(4) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, Ill., pp. 398–473, 1962.
(5) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, pp. 208–209, 1950.
(6) Smith, A. G. and G. Margolis, "Camphor Poisoning. Anatomical and Pharmacologic Study; Report of a Fatal Case; Experimental Investigation of Protective Action of Barbiturate," *American Journal of Pathology*, 30:857–869, 1954.
(7) OTC Volume 060008.
(8) OTC Volume 060009.
(9) OTC Volume 060029.
(10) OTC Volume 060030.
(11) OTC Volume 060031.
(12) OTC Volume 060040.
(13) OTC Volume 060050.
(14) OTC Volume 060051.
(15) OTC Volume 060054.
(16) OTC Volume 060062.
(17) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 249–252, 1957.

g. *Capsicum preparations (capsaicin, capsicum, capsicum oleoresin).* The Panel concludes that capsicum preparations (capsaicin, capsicum, capsicum oleoresin) are safe and effective for use as OTC external analgesics as specified in the dosage section below. The ingredients stimulate cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Capsicum is the dried, ripe fruit of *Capsicum frutescens Linne,* known in commerce as African chilies, or of *Capsicum annuum Linne var. conoides Irish,* known in commerce as tabasco pepper, or of *Capsicum annuum var. longum Sendt,* known in commerce as Louisiana long pepper, or of a hybrid between the Honka variety of Japanese capsicum and the old Louisiana sport capsicum known in commerce as Louisiana sport pepper (Fam. Solanaceae). Capsicum must be labeled to indicate which of the above varieties is contained in the package (Ref. 1). Capsicum was first referred to in 1494 by Chauca, a physician who accompanied Columbus on his second voyage to the West Indies (Ref. 1).

The action of capsicum is due to 0.1 to 1 percent capsaicin, a crystalline neutral principle that produces a persistent burning of the tongue in a dilution of 1:100,000 (Ref. 2). Capsicum oleoresin is a concentrate containing all of the active ingredients of capsicum, prepared by percolation of powdered capsicum with appropriate volatile solvents (Ref. 3).

Because of variations between lots of capsicum, the concentration range for this drug cannot be expressed in percentages but must be calculated for each lot from quantitative analytical data.

(1) *Safety.* Clinical use has confirmed that capsicum preparations (capsaicin, capsicum, capsicum oleoresin) are safe in the dosage range used as OTC external analgesics.

Capsicum is a powerful local stimulant. When swallowed, it produces a sensation of heat in the stomach, and a general glow over the body without any narcotic effect. Much used as a condiment, it has also been used for atony of the stomach or intestines (Ref. 4).

The toxicity of capsicum is low. Gastric administration of 28 mL of the oleoresin to fasting young rabbits caused diarrhea and loss of weight, followed by complete recovery; 56 mL was fatal (Ref.2).

Bevan reports that a reflex hypotensive response resulted following the injection of capsaicin (20 micrograms per kilogram (μg/kg)) in the pulmonary arterial tree of the cat. No significant difference was found when the injection was made into the right and left pulmonary arteries both distal to the bifurcation. The hypotensive response was almost absent when the injection was given into the right and left pulmonary hila. Following vagotomy, the hypotensive response disappeared. The results would indicate that sensory afferent endings stimulated by capsaicin are situated somewhere in the pulmonary artery and in the right and left branches proximal to the level of the hilus (Ref. 5).

In anesthetized dogs, intravenously injected capsaicin caused a transient apnea, bradycardia, and hypotension. Blood flow in the mesenteric, renal, and femoral arteries was decreased. However, that of the carotid artery was increased even in a small dose (10 to 25 mg; 45 mg/kg), causing changes in respiration, heart rate, and blood pressure. Cardiac muscle contractility was depressed principally, while capsaicin increased contractility of isolated guinea pig atrium. There is considerable shortening of the apneic phase and lack of bradycardia after vagi were cut. On the other hand, capsaicin caused a drastic increase in blood pressure and characteristic behavioral changes in the unanesthetized dog (Ref. 6).

Smith et al. (Ref. 7) undertook studies to determine whether the erythema and burning sensation caused by the application of capsaicin to human skin is related to lysosomal labilization. They compared its effects with cantharadin and Triton X-100™, both known lysosomal labilizers, on epidermal lysosomes and as vesicants to human glabrous skin. Patch testing of capsaicin 0.1 molar (M) produced erythema and a burning sensation in seven human subjects. The onset of the burning sensation was instantaneous in some cases and required up to 3 minutes to be established in others. Erythema was noted after 5 minutes and lasted up to 3 hours. Erythema was produced with 0.01 M capsaicin in six of the seven subjects and a burning sensation occurred in five of the seven subjects. Only one of the seven subjects developed erythema and a burning sensation with 0.001 M capsaicin applied to glabrous skin. No blisters or wheals were observed.

To summarize, the studies showed the following: Capsaicin produces erythema and a burning sensation without vesication when applied to the human skin. It also labilizes rat liver lysosomes but does not labilize rat epidermal lysosomes. Triton X-100™, a potent liver and epidermal lysosomal labilizer, does not produce blistering on human skin. Cantharides is a potent vesicant and liver lysosomal labilizer but does not labilize rat epidermal lysosomes. Thus, the hypothesis that blistering can result from primary labilization of epidermal lysosomes cannot be supported by experimental evidence from these studies (Ref. 7).

The safety of capsicum is well documented by marketing data. One product containing capsicum has sold more than 38,500,000 units and another in excess of 22,300,000 during the period 1960 to 1972 (Refs. 8 and 9). Another manufacturer reports annual sales of greater than 500,000 trade packages per year (Ref. 10). These manufacturers reported a total of 16 customer complaints for 1972 with none being of a serious nature.

(2) *Effectiveness.* There are studies documenting the effectiveness of capsicum preparations (capsaicin, capsicum, capsicum oleoresin) as OTC external analgesics. In addition, due to their wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that capsicum preparations are effective for use as OTC external analgesics.

When applied to the skin, preparations of capsicum extractions at first produce a sensation of warmth and, with greater concentration, eventually produce an almost intolerable burning sensation. Capsicum differs from other local irritants in producing practically no reddening of the skin even when there is a very severe subjective sensation. While it has a pronounced

irritant effect on the endings of sensory nerves, it has little action upon capillary or other blood vessels. Therefore, it does not cause blistering, even in high concentrations (Ref. 4).

Peterson et al. (Ref. 10), in their study of responses of the skin to counterirritants (rubefacients), applied nine different conterirritants, including 5 percent tincture of capsicum, to the skin of five human subjects. The skin of the upper back was used for the application of the counterirritant ointments. Eighty mg of each counterirritant ointment preparation was applied with the same technique. Thereafter, the degrees of erythema and skin temperature of each site were observed at 5-minute intervals for a minimum of 30 minutes. The Sargent Thermistor unit recorded changes in skin temperature. Erythema was graded 0 to 3+ (1+ for slight erythema, 2+ for moderate, and 3+ for marked erythema). Several of the preparations which evoked no erythema or temperature elevation included 5 percent tincture of capsicum along with tincture of cantharides, methyl salicylate, Peruvian balsam, and Unibase ™ control. Those producing erythema and temperature changes were nicotinic acid, tetrahydro-furfuryl ester of nicotinic acid, camphor, and mustard oil. The quantitative inunction of counterirritant ointments had little or no effect on the cutaneous response of the subject using other counterirritants, e.g., methyl nicotinate, that did produce erythema. The degree of rubor and the temporal development of rubor were unaffected by the gradation of inunction. Graded inunction resulted in only minor deviation in degree of skin temperature elevation and likewise in temporal development of same. The skin temperature elevations evoked by counterirritants seem to parallel quantitatively the extent of erythema produced. Maximal erythema usually precedes maximal temperature rise by several minutes (Ref. 5).

Although capsicum and its derivatives are powerful counterirritants, they do not have rubefacient activity. They produce practically no redness and have little effect upon the capillaries or other blood vessels. The therapeutic effectiveness of topically administered capsicum or its derivatives has not been adequately studied. However, the sensation of warmth produced upon application is an important consideration which is highly acceptable to the patient.

In all submissions to the Panel, either capsicum oleoresin or capsaicin was employed in combination with other counterirritant ingredients in a manner considered both rational and appropriate by the Panel (Refs. 9 through 12).

Capsicum preparations have been effectively used as OTC external analgesics in concentrations of 0.025 to 0.25 percent capsaicin, or an equivalent concentration of capsicum or capsicum oleoresin.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.025 to 0.25 percent concentration capsaicin, or a percent concentration of capsicum or percent concentration of capsicum oleoresin that yields the equivalent of 0.025 to 0.25 percent concentration capsaicin, to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Claus, E., V. Tyler, and L. Brady, "Pharmacognosy," 6th Ed., Lea and Febiger, Philadelphia, pp. 211–212, 1970.

(2) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders and Co., Philadelphia, p. 162, 1957.

(3) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 216, 1950.

(4) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 223, 1973.

(5) Bevan, J. A., "Action of Lobeline and Capsaicine on Afferent Endings in the Pulmonary Artery of the Cat," *Circulation Research,* 10:792–797, 1962.

(6) Neno, A., "Cardiovascular Action of Capsaicin in Dogs and Unanesthetized Dogs with Radiotelemeter Folio," *Pharmacology (Japanese),* 67:572–579, 1971.

(7) Smith, J. G., R. G. Crounse, and D. Spense, "The Effects of Capsaicin on Human Skin, Liver, and Epidermal Lysosomes," *Journal of Investigative Dermatology,* 54(2):170–173, February, 1970.

(8) OTC Volume 060030.

(9) OTC Volume 060033.

(10) OTC Volume 060077.

(11) OTC Volume 060031.

(12) OTC Volume 060040.

h. *Dibucaine.* The Panel concludes that dibucaine is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Dibucaine is a synthetic topical anesthetic of the "caine" type, derived from quinoline (Ref. 1). It was introduced in 1929 by McElwain (Refs. 2 and 3). Its chemical name is butyl oxychinchoninic acid diethyl ethylenediamide. It is in no way related to quinine as its name may suggest. Thus, it is not an ester but an amide. It was one of the first of the amides to be adopted for clinical use. Its chemical configuration follows closely the general characteristics of the "caine" type of drugs (Refs. 2 and 4).

Dibucaine is a tertiary amine and, therefore, a base that reacts with acids to form salts, the most common of which is the hydrochloride. The free base is a colorless or almost colorless powder that melts at 63° to 64° C. The powder darkens on exposure to air. As is the case with other bases of the topical anesthetics of the "caine" type, it is poorly soluble in water. It is readily soluble in ether and various other organic solvents, in fatty oils, and in oleaginous bases.

The hydrochloride salt is a white, tasteless powder which melts at 90° to 98° C. The melting point is not sharp. It is very soluble in water (one part dissolves in 0.5 part water) and in organic solvents such as benzene, acetone, and chloroform. It is insoluble in ethers and oils. Aqueous solutions have pH range of 6.2 to 6.5. Alkaline substances such as hydroxides, carbonates, and bicarbonates readily precipitate the base from aqueous solutions. Solutions must be prepared in distilled water and stored in alkaline-free glass; otherwise, the drug will precipitate out due to the action of alkali in the glass. Solutions of salts of dibucaine are stable when boiled. Dibucaine is compatible with epinephrine. Dibucaine has also been marketed under such names as percain (British), chinchocaine sovcaine, benzoline, and cincaine. The U.S.P. name and the one that is accpeted is dibucaine. The hydrochloride salt is more stable than the base (Refs. 1, 2, 4, and 5). The salt is poorly soluble in oils or nonwater-soluble bases but soluble in glycols.

(1) *Safety.* Clinical use has confirmed that dibucaine is safe in the dosage range used as an OTC external analgesic.

Dibucaine is a synthetic amide type topical anesthetic derived from quinoline (Refs. 2 and 6). It is a base that forms salts with various acids. The most frequently used salt is the hydrochloride. Dibucaine is a "caine" type drug and closely follows the chemical configuration of " caine" type drugs in having an amino group, dimethylene chain, and aromatic nucleus. Dibucaine is one of the most potent and longest lasting of the topical

anesthetics. Dibucaine is approximately 15 times more potent and toxic than procaine, which has been used as the reference standard in clinical studies. Consequently, only one-fifteenth as much dibucaine would be required to achieve the same effect as a given amount of procaine. The absolute toxicity is 15, but the relative toxicity compared to procaine is 1. Toxicity, of course, depends upon the site and mode of application, and the vascularity of the tissues as well as the mode and rate of biotransformation. The lethal dose in man, therefore, is unknown. In mice, the acute LD_{50} intravenously is 2.8 mg/kg compared to 21 mg/kg, for procaine and 11 mg/kg for cocaine. In rabbits, intravenous dibucaine is six times as toxic as cocaine (Ref. 7). Dibucaine produces central nervous system stimulation and myocardial depression characteristic of the "caine" type of drugs when recommended doses are exceeded and high plasma levels result. Fatalities have been reported from use of the maximal tolerable dose following infiltration, perineural injection, or topical application to the mucous membranes. Ten cases of acute intoxication in children were reported after oral ingestion of topical preparations. Four were fatal. Six children survived the reaction to the overdose. An additional case was reported after rectal use of an ointment marketed for OTC rectal use. This case was a fatal reaction following rectal instillation in a 2-month-old infant. These cases were documented in an adverse reaction reporting system extending from 1951 to 1972 (Ref. 8).

During the long period of marketing experience, cutaneous reactions due to irritancy and allergy have been low. Patch testing in controlled studies in man and a review of the literature by Lane and Luikart (Ref. 9) reveal that the incidence of sensitization reactions is low and no greater than that observed with procaine, tetracaine, benzocaine, and cylcomethycaine (Ref. 9). Dibucaine can act as a haptene and be antigenic. Anaphylactic and other allergic-type reactions are possible but have not been reported after topical use.

Dibucaine has been regarded as a toxic anesthetic by physicians. Relatively speaking, however, it is no more toxic than procaine, tetracaine, lidocaine, and similarly acting drugs. Dibucaine's chief danger lies in its potency, because one-tenth to one-fifteenth as much of it would be required as of lidocaine or procaine. Although systemic reactions from application to the intact skin are uncommon, it could be obsorbed if used too liberally in topical application over wide areas of damaged or abraded skin or mucous membranes. This systemic absorption may result in convulsions, myocardial depression, and death (Ref. 5).

Dibucaine must not be ingested orally because it is absorbed from the intestines. Fatalities have been reported from accidental ingestion by children. Sensitization can occur but is uncommon. Marketing history shows 2.6 cases of adverse reactions per million units sold (Ref. 8).

(2) *Effetiveness.* There are studies documenting the effectiveness of dibucaine as an external analgesic.

Dibucaine is one of the most potent and longest lasting topical anesthetics. It is approximately 15 times more potent than procaine and 3 to 6 times more potent than cocaine. Like other topical anesthetics, dibucaine acts by stabilizing the neuronal membrane of the pain receptors in the skin. It has been used extensively for spinal anesthesia, topical anesthesia on the mucous membranes and skin, and to a lesser extent, for infiltration and nerve blocking. Its period of latency when used intrathecally may be as long as 10 minutes. Its duration of action intrathecally is approximately 3 hours. This latency and long duration are also manifested when dibucaine is used by other routes (Ref. 2).

Adriani and Dalili (Ref. 10) noted that a concentrated solution in propylene glycol, alcohol, and water obtunded the response of receptors for pain and itch within 15 minutes. This effect lasted as long as a moist film remained on the skin, which was as long as 4 hours in some cases. When the film was wiped from the skin, response to the stimulation was reestablished within 15 minutes.

Dibucaine base readily penetrates the intact skin. Its action on the skin is superficial because it acts on the cutaneous receptors and remains in direct contact continuously when incorporated in a suitable medium that provides a film that remains moist. The concentrations absorbed systemically from the skin are insufficient to relieve pain in subcutaneous structures or in muscles, tendons, or other deeper structures. It is suitable, therefore, only for those situations involving pain, burning, or itching of the skin as specified in the labeling section below. The usual effective dosage range applied topically on the skin is 0.25 to 1 percent.

(3) *Dosage—For adults and children 2 years of age or older:* Apply a 0.25 to 1.0 percent concentration of dibucaine to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

References

(1) Adriani, J., "Local Anesthetics," *in* "The Pharmacology of Anesthetic Drugs," 5th Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 131–145, 1970.

(2) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(3) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 990, 1975.

(4) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 413, 1973.

(5) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(6) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(7) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 435, 1955.

(8) OTC Volume 060013.

(9) Lane, C. G. and R. Luikart, "Dermatitis from Local Anesthetics with a Review of One Hundred and Seven Cases from the Literature," *Journal of the American Medical Association,* 146:717–720, 1951.

(10) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

i. *Dibucaine hydrochloride.* The Panel concludes that dibucaine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

The general characteristics of dibucaine hydrochloride have been discussed elsewhere in this document. (See part III. paragraph B.1.h. above—Dibucaine.)

(1) *Safety.* Clinical use has confirmed that dibucaine hydrochloride is safe in the dosage range used as an OTC external analgesic.

The remarks above concerning the safety of dibucaine base are also applicable to the hydrochloride. (See part III. paragraph B.1.h.(1) above—

Safety.) As with other topical anesthetics, dibucaine hydrochloride penetrates damaged epithelial barriers and exerts an analgesic effect on pain receptors and other receptors in the skin and on receptors in structures immediately beneath the epithelial layers. It passes into the tissue fluids and gains access to the systemic circulation. Even though dibucaine hydrochloride is about 15 times more potent and toxic than procaine, a proportional reduction in the quantity used results in a hazard no greater than that found with other local anesthetics. Therefore, reactions from the use of therapeutic doses on the skin are uncommon.

Systemic absorption may result in convulsions, myocardial depression, and death (Ref. 1). Dibucaine hydrochloride is absorbed from open lesions and damaged and abraded skin, but not from the intact epithelial barriers (Refs. 2 and 3). The possibility that sufficient quantities may be absorbed from extensive areas of damaged skin exists. The Panel, therefore, recommends that statements to this effect be included in the labeling and that the use of dibucaine hydrochloride preparations be restricted to areas not exceeding 25 percent of the body surface. Obviously, a statement defining areas of body surface will have little meaning to users of OTC products in most cases. Because the hydrochloride is more soluble in the water of tissue fluids than is the base, the Panel calls attention to the greater hazard that exists from the rapid absorption from damaged skin and the greater possibility of systemic reactions when hydrochloride preparations are used.

Sensitization has been reported but is uncommon.

(2) *Effectiveness.* There are studies documenting the effectiveness of dibucaine hydrochloride as an OTC external analgesic. In addition, due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that dibucaine hydrochloride is effective for use as an OTC external analgesic.

When absorbed by the buffering mechanisms in the tissues, dibucaine hydrochloride is converted to the base (Ref. 4). Its mechanism of action is similar to dibucaine base. Dibucaine hydrochloride penetrates the intact skin so slowly that quantities absorbed are not effective. Adriani and Dalili (Ref. 5) reported that the sensation of pain and itch elicited by electrical stimulation of the skin were not obtunded by application of 1 to 2 percent ointments and creams containing dibucaine hydrochloride. They also noted that these same preparations afforded no relief to the burning and itching sensation of both intact and damaged skin that had been exposed to ultraviolet light. On the other hand, saturated solutions of the base in 40 percent propylene glycol, 20 percent alcohol, and 40 percent water were effective and abolished both the discomfort and the ability of receptors in this area of skin to respond to electrical stimulation that had continued to exist when the hydrochloride preparations were used. On damaged skin, dibucaine hydrochloride is as effective as the base in concentrations ranging from 0.25 to 1.0 percent. Claims for effectiveness on the intact skin cannot be made for any of the salts (Ref. 5). Therefore, the Panel does not recommend a dose for use on the intact skin.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.25 to 1.0 percent concentration of dibucaine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

References

(1) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Parctitioner,* 25:82–86, 1962.

(2) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(3) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(4) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp 398–473, 1962.

(5) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

j. *Dimethisoquin hydrochloride.* The Panel concludes that dimethisoquin hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Dimethisoquin is an aminoethoxy derivative of isoquinoline (Refs. 1 and 2). It is chemically allied to dibucaine, which is a quinoline derivative, but differs from dibucaine because dimethisoquin is derived from isoquinoline and is not an amide. Also, dimethisoquin differs from other local anesthetics in that it is a modification of the configuration common to the "caine" type drugs. The dimethylene chain or pivot is linked to the 2 position of the isoquinoline nucleus by an ether linkage. It is a tertiary amine having 2 methyl groups in addition to the main portion of the molecule on a nitrogen atom. Dimethisoquin is, therefore, a base that combines with acids to form salts, the most important of which is the hydrochloride. The base is a liquid that boils between 155° to 157° C. The hydrochloride, the ingredient used in OTC preparations, is a white crystalline powder. One g dissolves in approximately 8 mL of water, 3 mL of alcohol, and 2 mL of chloroform. It is very slightly soluble in ether. The crystals of the salt melt at approximately 146° C (Refs. 2 and 3). It has also been known as isochinol, pruralgen, and pruralgin.

(1) *Safety.* Clinical use has confirmed that dimethisoquin hydrochloride is safe in the dosage range used as an OTC external analgesic.

The oral LD_{50} of dimethisoquin hydrochloride in rats in approximately 250 mg/kg. Intraperitoneally the LD_{50} is 45 to 50 mg/kg; intravenously the LD_{50} ranges between 4.5 to 5.0 mg/kg. It is far less toxic than dibucaine. Comparable doses of dibucaine are within a 2.0 to 2.5 mg/kg range. In rabbits, the LD_{50} of dimethisoquin hydrochloride administered intravenously was 4 to 6 mg/kg, compared with the LD_{50} of dibucaine, which was 2.0 to 2.5 mg. In dogs anesthetized with sodium pentobarbital, dimethisoquin caused cardiac and respiratory depression. Because the barbiturate nullifies the central nervous system stimulating effects of local anesthetics, it could not be determined from these studies whether dimethisoquin causes convulsions.

Chronic toxicity studies of dimethisoquin hydrochloride were done in which relatively large quantities of the drug were administered intraperitoneally to guinea pigs for a period of 30 days, after which the animals were sacrified. The tissues were examined histologically. No discernible pathologic changes were found that could be attributed to the tested substance (Ref. 5). Similar studies in

guinea pigs were likewise negative as far as histological examinations were concerned (Ref. 5).

Convulsions, cardiac depression, and other manifestations of local anesthetic toxicity characteristic of the "caine" type drugs have not been observed or reported in humans.

In the early clinical studies of dimethisoquin hydrochloride, it was administered in lozenges containing 5 to 7 mg of the drug to 254 patients for various pharyngeal and laryngeal infections that were accompanied by pain. The drug was also administered to patients with peptic ulcers. No evidence of systemic toxicity with dimenthisoquin was observed after oral ingestion. Marketing experience reveals a lack of data on any adverse reactions in humans. Since the marketing of dimethisoquin, there were no reports from 1951 to 1972 of any reactions attributed to the topical anesthetic.

There is no significant data indicating that dimethisoquin causes any local irritancy when applied as an ointment or a lotion to the skin and mucous membranes. Dimethisoquin hydrochloride-containing preparations have a low sensitizing potential. Only 4 cases of sensitivity were reported to the manufacturer in over 2,200 cases (Ref. 5). Two were believed to be due to the vehicle rather than to the active ingredients. Two other cases of sensitivity reactions of dimethisoquin hydrochloride ointment have been reported in the literature since the products were marketed (Ref. 5). One patient had a patch test that was positive to dimethisoquin hydrochloride. In the other case that was reported it was undetermined whether the patch test was due to the material in the ointment or to the active ingredient itself. Since dimethisoquin hydrochloride can act as a haptene, the possibility that allergic reactions may occur cannot be discounted, but the extensive marketing experience, in the opinion of the Panel, indicates that allergy is not a problem of any magnitude or seriousness.

Fellows and Macko (Ref. 6) conducted studies of the inhibition of cell growth by various topical anesthetics using human epidermis. They reported that the order of increasing inhibition of cell growth is saline, procaine, boric acid, resorcinol, dimethisoquin, dibucaine, and mercuric chloride.

(2) *Effectiveness.* There are studies documenting the effectiveness of dimethisoquin hydrochloride as an OTC external analgesic.

Dimethisoquin hydrochloride is effective topically on the mucous membranes and on abraded and scarified skin. Fellows and Macko (Ref. 6) reported that dimethisoquin hydrochloride was 1,000 times more active than cocaine and 10 times more active than dibucaine when applied to the cornea of rabbits. The intradermal potency was found to be 100 times greater than procaine. Although these studies do not establish its effectiveness on the intact and damaged (broken) skin, they do establish that dimethisoquin possesses topical anesthetic activity.

Adriani et al. (Ref. 4) also observed that dimethisoquin possessed topical anesthetic activity when applied to the tip of the tongue. The duraton of action was less than 10 minutes, compared to 50 minutes for dibucaine. Anesthesia was only partial, and complete obtundation was not obtained. Complete abolition of the sensation or pain induced by electrical stimulation was not obtained even with potent drugs such as cocaine, tetracaine, dibucaine, lidocaine, and others. These subjects, however, felt numbness in other areas of the oral cavity. Because the tip of the tongue appears to these investigators to be more difficult to anesthetize, they conceded that dimethisoquin does possess topical anesthetic activity, but not to the degree that corneal anesthesia in the rabbit would suggest.

Whether dimethisoquin hydrochloride penetrates the intact (unbroken) skin is debatable, because this does not appear to be so with other topical anesthetics that are more potent and more effective when applied directly to nerve tissues. Studies on the penetration of the base (dimethisoquin) of this derivative are not available.

Dimethisoquin is not used for perineural injection. Its mode of action is presumed to be similar to that of the other nitrogen-containing anesthetics, i.e., by stabilization of the neuronal membrane. There are an adequate number of claims for effectiveness for the relief of pruritus and painful conditions of the skin based on subjective studies. (Reports are available on over 1,700 patients with various forms of dermatitis and proritus treated with dimethisoquin hydrochloride ointment and lotion (Ref. 6)). In most cases, the concentration of dimethisoquin hydrochloride in the preparation was 0.5 percent, although some of the early investigations used both lower and higher concentrations in an attempt to determine the most effective and least irritating level.

The most extensive experiences with dimethisoquin hydrochloride ointment and lotion have been those of the group at the Hospital of the University of Pennsylvania under the direction of D. M. Pillsbury. In 1952, this group prepare a report detailing experiences with 1,00 patients who had been treated with dimethisoquin preparations over a period of 3 years. The investigators stated that "in a strength of 0.3 to 0.5 percent dimethisoquin hydrochloride ointment produced the relief of pruritus in 85 to 90 percent of the patients to whom the treatment was given. This is approximately 20 percent more than obtained any degree of relief from the ointment base alone" (Ref. 5).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.3 to 0.5 percent concentration of dimethisoquin hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(2) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 436–437, 1973.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 427, 1976.

(4) Adriani, J., R. Zepernick, J. Arens, and E. Authement, "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

(5) OTC Volume 060026.

(6) Fellows, E. J. and E. Macko, "The Topical Anesthetic Activity of an Isoquinoline Compound," *Journal of Pharmacology and Experimental Therapeutics,* 103:306–309, 1951.

k. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Diphenhydramine is an amine derived from ethylene diamine. It is a base that forms a salt with hydrochloric acid (Refs. 1 and 2). Diphenhydramine possesses various pharmacologic actions which include anticholinergic, antihistaminic, antiemetic, topical anesthetic, and hypnotic activities. It is used orally, intravenously, and topically. It is most effective when used systemically.

Diphenhydramine hydrochloride occurs as a white, odorless, crystalline powder. It slowly darkens on exposure to light. The solution is practically neutral to litmus. One g dissolves in 1 mL water, 2 mL alcohol, 2 mL chloroform, and 50 mL acetone. It is very slightly soluble in benzene and in ether. Diphenhydramine hydrochloride melts between 166° and 170° C.

Diphenhydramine was the first antihistaminic drug available in the United States. It has served as a standard for comparison in the study of the many other antihistamines now available. In 1945, Loew et al. (Ref. 3) applied the antihistaminic concept by using diphenhydramine as an antagonist to histamine. Its efficacy in the relief of urticaria was demonstrated by Curtis and Owens (Ref. 4), and its effectiveness in hay fever and vasomotor rhinitis, by others (Refs. 5).

(1) *Safety.* Clinical use has confirmed that diphenhydramine hydrochloride is safe in the dosage range used as an OTC external analgesic.

If drowsiness is included, the incidence of side effects obtained with the systemic use of diphenhydramine hydrochloride is high, being 46 percent of 1,210 patients reported by Sachs (Ref. 6), 61 percent of 655 cases reported by Loveless (Ref. 7), and 77 percent of 52 cases reported by McGavic et al. (Ref. 8). If drowsiness is excluded, the incidence of side effects is low. Other side effects include dizziness, dry mouth, lassitude, and nausea. In ambulatory patients, drowsiness and dizziness create an accident-causing hazard due to impaired psychomotor function. Despite its sedative and hypnotic effect, diphenhydramine hydrochloride has no tendency to cause dependence. Asthmatic seizures have been precipitated by diphenhydramine hydrochloride in some asthmatics after oral or parental use. Barbiturate and other hypnotic sedation is prolonged when used concomitantly with diphenhydramine hydrochloride, orally or parenterally.

Toxic doses in animals produce a complex syndrome predominately neurogenic in origin, involving the motor, sensory, and autonomic nervous systems (Ref. 9). Manifestations include excitement, irritability, spastic ataxia, mydriasis, hyperesthesia, and convulsions. Respiratory and cardiac failure may result from massive overdosage.

Death of a 2-year-old child following accidental ingestion of 474 mg diphenhydramine hydrochloride has been reported (Ref. 10). The symptoms included lethargy, coma, shallow respiration, and cyanosis followed by nervousness, twitching, convulsions, fever, and tachycardia. The child died 13 hours later. A 3-year-old child who accidentally swallowed 780 mg diphenhydramine hydrochloride recovered. When convulsions occur after ingestion of diphenhydramine hydrochloride, they are of the intermittent clonic type. The pupils become dilated and fixed. Coma associated with apnea, cyanosis, and vascular collapse develops.

Studies of the metabolism of diphenhydramine hydrochloride in rats and guinea pigs reveal that the highest concentration of the drug is found in the lung, spleen, and liver 1 hour after oral or parenteral administration. After 6 hours, little can be found in the animal. Only 5 to 15 percent of a dose can be found unchanged in the urine in 24 hours. Studies of the drug labeled with radioactive carbon ^{14} indicate that degradation products are formed and excreted in the urine. The tissue presence of enzymes that have such a degrading action was demonstrated by Glazko and Dill (Ref. 11).

Diphenhydramine hydrochloride is absorbed from damaged skin and, like other drugs absorbed from the skin, gains access to the blood stream. In view of diphenhydramine hydrochloride's low degree of toxicity when used orally or parenterally, the Panel does not consider systemic toxicity from topical application to be a question of major importance. The Panel is unaware of any instance of systemic toxicity reported from the topical use of diphenhydramine hydrochloride. The incidence of topical irritancy is low. The Panel does caution that diphenhydramine hydrochloride can act as a haptene and cause sensitization and systemic as well as topical allergic manifestations, particularly after repeated frequent use.

The increasing incidence of acquired sensitivity to the antihistaminic creams is discussed by Ellis and Bundick (Ref. 12). These authors indicate that the antipruritic action of topical antihistaminic drugs is most useful for 1 to 2 weeks to prevent continued trauma of scratching and to permit permanent healing. However, the loss of efficacy is frequent after using the drugs for 3 to 4 weeks. Sensitivity often develops after this period of use. The Panel does not recommend use for longer than 7 days except under the advice and supervision of a physician.

(2) *Effectiveness.* There are studies documenting the effectiveness of diphenhydramine hydrochloride as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that diphenhydramine hydrochloride is effective for use as an OTC external analgesic.

Diphenhydramine hydrochloride and other antihistaminic drugs are specific blocking agents that when administered systemically, diminish or abolish the effects of histamine on smooth muscle and in the exocrine glands (Refs. 1, 13, and 14). They inhibit the spasmogenic action of histamine on smooth muscle in the uterus. Diphenhydramine hydrochloride prevents histamine from increasing the permeability of capillary endothelium and inhibiting the vasodilating action on the capillaries. In therapeutically effective doses, diphenhydramine does not inhibit the stimulating action of histamine on gastric secretion. The antiallergic reaction of diphenhydramine hydrochloride is due to its antagonistic effect on histamine. It binds at cell receptors for histamine, thereby preventing histamine from acting on a cell because the cell receptor is already occupied when histamine is released. This is the rational basis for its use as a prophylactic agent (Ref. 14). Therapeutic doses have no significant effect on the blood pressure, heart, and gastrointestinal tract. Diphenhydramine hydrochloride protects the body from the effects of both exogenous and endogenous histamine (Ref. 14).

Diphenhydramine hydrochloride does not overcome the various physiologic responses to histamine by an opposing pharmacologic action as is the case with epinephrine, aminophylline, and other drugs. Diphenhydramine hydrochloride provides symptomatic relief in allergic disorders by protecting the cells from the effects of free histamine released from pathologic conditions. Any effect antihistamines exert topically is due to their antagonistic effect on histamine. Histamine may be released in the skin and subcutaneous structures due to the action of allergen-antibody responses, and from trauma due to mechanical, chemical, and other causes. It is generally conceded that if the receptors are occupied by histamine, the antihistamine cannot act. Diphenhydramine hydrochloride has a feeble anticholinergic and topical anesthetic effect (Ref. 15). The anticholinergic effect is of no consequence in considering topical use. Diphenhydramine hydrochloride acts in the same manner as do topical anesthetics and does not penetrate the epithelial barrier when the drug is applied to the intact skin (Ref. 1).

Diphenhydramine hydrochloride is used orally, parenterally, and topically

for the symptomatic treatment of urticaria, hay fever, and other allergic disorders caused by histamine. Diphenhydramine hydrochloride has considerable sedative action that is utilized orally or parenterally where sedation is therapeutically useful, but should be avoided in individuals engaged in hazardous activities. Sedation is not a problem of concern when the drug is used topically on the skin in localized areas of the body. Diphenhydramine hydrochloride has been effectively used as a topical antipruritic ingredient in concentrations ranging from 1 to 2 percent (Ref. 16).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 to 2 percent concentration of diphenhydramine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredient. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 441–442, 1973.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 442, 1976.

(3) Loew, E. R., M. E. Kaiser, and V. Moore, "Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine," *Journal of Pharmacology,* 83:120–129, 1945.

(4) Curtis, A. C. and B. B. Owens, "Beta Diphenhydramine Benzhydryl Ether Hydrochloride (Benadryl) in Treatment of Urticaria," *Archives of Dermatology and Syphilology,* 52:239–242, 1945.

(5) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1060–1061, 1975.

(6) Sachs, B. A., "The Toxicity of Benadryl: Report of a Case and Review of the Literature," *Annals of Internal Medicine,* 29:135–144, 1948.

(7) Loveless, M. H., "Therapeutic and Side Effects of Pyribenzamine and Benadryl, A Comparative Study Based Upon a Survey of 26 Clinical Reports in the Literature," *American Journal of Medicine,* 3:296–308, 1947.

(8) McGavack, T. H., J. Weissbergh, and L. I. Boyd, "Comparison of the Toxic Manifestations Produced by Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) and Tripelennamine (Pyribenzamine)," *Journal of Laboratory and Clinical Medicine,* 33:595–601, 1948.

(9) Gruhzit, O. M. and R. A. Fisken, "A Toxicologic Study of Two Histamine Antagonists of the Benzhydryl Alkamine Ether Groups," *Journal of Pharmacology,* 89:227–233, 1947.

(10) Davis, V. H. and M. H. Hunt, "Accidental Benadryl Poisoning: Report of a Fatal Case," *The Journal of Pediatrics,* 34:358–361, 1949.

(11) Glasko, A. J. and W. A. Dill, "Biochemical Studies on Diphenhydramine (Benadryl) Distribution in Tissues and Urinary Excretion," *Journal of Biological Chemistry,* 17:403–408, 1949.

(12) Ellis, F. A. and W. R. Bundick, "Appraisal of Topical Use of Antihistamines," *Journal of the American Medical Association,* 150:773–776, 1952.

(13) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 1090–1098, 1977.

(14) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 146–150, 1973.

(15) Adriani, J., R. Zepernick, J. Arens, and E. Authement, "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

(16) OTC Volume 060095.

1. *Dyclonine hydrochloride.* The Panel concludes that dyclonine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Dyclonine does not conform to the general configuration of the commonly used topical anesthetics of the "caine" type drugs, such as lidocaine and tetracaine (Ref. 1). Dyclonine is a propiophenone derivative. One end of the dimethylene chain of the ketone is attached to the nitrogen atom of the piperidine group of the first carbon atom which carries the ketonic group. This is attached directly to a benzene ring which is attached to a butoxy group in the para position. Thus, unlike procaine and lidocaine, it is neither an amide nor an ester, nor can it be considered an ether, as is the case with pramoxine. Dyclonine is a base that forms salts with hydrochloric acid (Ref. 2).

Dyclonine hydrochloride is a white crystalline powder. One g dissolves in approximately 50 mL water. It is soluble in acetone, alcohol, and chloroform. The crystals melt at between 173° to 178° C. It is also soluble in washable cream bases. The chemical name is 4-*n*-butoxy-*beta*-piperidinopropiophenone hydrochloride (Ref. 2).

(1) *Safety.* Clinical use has confirmed that dyclonine hydrochloride is safe in the dosage range used as an OTC external analgesic.

Although dyclonine is a nitrogenous base, its chemical structure departs from that of the "caine" type drugs (Refs. 2 and 3). For this reason, acute systemic toxicity characterized by convulsions, myocardial depression, hypotension, etc., which are characteristic of the so-called "caine" type drugs, do not occur.

The acute LD_{50} for dyclonine hydrochloride was studied by Abreu and associates (Ref. 4) in dogs and albino rats. In rats, the LD_{50} intraperitoneally was approximately 45.8 mg/kg, and in dogs, the LD_{50} was approximately 9.5 mg/kg. Abrue also noted that in anesthetized dogs, doses of 2 mg/kg intravenously did not significantly affect blood pressure or pulse, nor did they reduce the cardiovascular response to acetylcholine. They also did not increase the response to epinephrine, as demonstrated by a lack of parasympatholytic activity. Doses of 5 mg/kg in anesthetized dogs may cause respiratory failure, but this is reversible and the animals recover if respiration efforts are used.

The cardiovascular effects of dyclonine were investigated in dogs anesthetized with sodium barbital. The drug was administered over a 25-second period with a dose range of 0.25 to 10 mg/kg in 10 dogs. Dyclonine lowered arterial pressure approximately 10 mm mercury at a dose of 1 mg/kg. There was a progressive increase in response at doses of 1, 2, 3, 4, and 5 mg/kg with death being produced at a dose of 10 mg/kg. The mechanism of this reduction in activity was due to a decrease in cardiac output as well as to peripheral arterial dilatation. Initially, dyclonine hydrochloride induces some respiratory stimulation when the drug is administered intravenously to dogs. As the dosage is increased, depression of respiration and oxygen consumption occurs. Dyclonine was demonstrated to act as an anticonvulsant, a multisynaptic and spinal reflex depressant of the central nervous system (Ref. 5).

Chronic toxicity studies were done with dyclonine hydrochloride in the albino rat and in the dog. Dyclonine hydrochloride did not significantly affect the growth rate of male or female weanling albino rats as compared to controls when it was administered intraperitoneally for 30 consecutive days. A total of 48 rats divided evenly as to sex, drug groups, and controls were employed using one-fourth and one-half the intraperitoneal LD_{50} of the adult rat. At the end of the experimental period, half the animals were sacrificed, at which time no gross pathologic changes were observed. When mated, the drug-treated survivors did not differ from controls in their reproductive

capacity. Upon weaning, the offspring of the first group, when subjected to the same experiment, also did not differ from their controls either in growth rate or reproductive capacity. No gross pathologic changes were observed in these animals when sacrificed. Experimental observations in dogs given doses varying from 5 to 12 mg/kg twice daily likewise showed no gross pathologic changes, intramuscularly or subcutaneously. No significant changes from normal were noted in hemoglobin concentration, red and white blood cell counts, and white cell differential counts which were measured at biweekly intervals (Ref. 5).

In man, dyclonine hydrochloride possesses a relatively low degree of toxicity. When the ingredient was applied topically to the skin of 3,656 patients in the form of a cream and to 2,000 additional cases in the form of a solution for topical anesthesia, only 2 cases of proven sensitivity were reported. It was concluded from these studies that the sensitizing potential of dyclonine hydrochloride under conditions of clinical use is low. In a study using a dyclonine hydrochloride solution, no adverse effects were found.

In a study dealing with the safety of dyclonine hydrochloride following oral administration, 35 patients were given from 300 to 600 mg daily for periods of time varying from 1 to 12 weeks. No undesirable side effects occurred. It was concluded that the compound would be entirely safe for human consumption (Ref. 5). Adriani and Campbell (Ref. 6) emphasized that the two safest topical anesthetics for use on the mucous membranes for endoscopic procedures are benzocaine and dyclonine hydrochloride, because they show the lowest incidence of systemic reactions.

(2) *Effectiveness.* There are studies documenting the effectiveness of dyclonine hydrochloride as an OTC external analgesic.

Dyclonine hydrochloride is a highly effective topical anesthetic, particularly on mucous surfaces and on the abraded and damaged skin. Although it is also an effective nerve-blocking agent, it is irritating and may produce slough in the tissue. It is, therefore, recommended for topical use only. Dyclonine hydrochloride blocks transmission at nerve endings in the same manner as do other topical anesthetics closely related to, or of, the "caine" type drug. Dyclonine is a base and, like other topical anesthetics, is not absorbed through the intact skin. The base is unstable. The product is marketed as a salt (hydrochloride). Dyclonine hydrochloride is not absorded through the intact skin in quantities sufficient to produce analgesia. In studies on mucous membranes conducted by Adriani, Zepernick, and co-workers (Ref. 7), dyclonine ranked fourth (after dibucaine, cocaine, and tetracaine) in effectiveness in producing analgesia. One percent dyclonine produced analgesic action of 27 minutes, with a latent period of 2 to 3 minutes. The fact that dyclonine is effective on the mucous membranes is established. Dalili and Adriani (Ref. 8) noted that a 1-percent solution of the hydrochloride did not obtund the effect of electrical stimulation while eliciting the sensation of burning and itching on the skin. When the skin was burned with ultraviolet light, the application of the solution produced an exaggeration of the discomfort rather than relief (Ref. 7). Concentrations as low as 0.5 percent have been found to be effective as a topical analgesic on damaged skin.

Morginson et al. (Ref. 5) observed the antipruritic proper ties of a 1-percent dyclonine hydrochloride cream in a study of 222 patients with various forms of dermatoses. The preparation was effective in controlling pruritus in 127 (57 percent) of the patients and was without effect in 95 patients (43 percent). A 1-percent dyclonine hydrochloride cream and also the vehicle without dyclonine hydrochloride were used in paired studies in 33 patients (Ref. 5). The dyclonine hydrochloride cream produced relief from itching in every case. No relief was produced by the vehicle alone.

Employing a double-blind study, Orentreich, Berger, and Auerbach (Ref. 5) evaluated the degree of anesthetic effect of a 1-percent dyclonine hydrochloride cream used on 58 patients with various pruritic and/or painful dermatoses. Thirty patients showed improvement, 4 patients became worse, and 24 patients showed no change.

Marks conducted a study of the effect of 1 percent dyclonine hydrochloride cream in post-anorectal surgical patients throughout the healing period (Ref. 5). The anesthetic action of the 1-percent dyclonine hydrochloride preparation was prompt and satisfactory, with wounds remaining clean. Waterlogging was absent, and granulations were firm with rapid epithelialization.

Gomez observed the anesthetic action of a 1-percent dyclonine hydrochloride cream on 50 patients who had undergone episiotomies (Ref. 5). The effects of the 1-percent dyclonine hydrochloride cream were compared with the effects produced by known topical anesthetics in 25 other patients who had undergone episiotomies. Further comparison was made, under similar circumstances, between the effects of the 1-percent dyclonine hydrochloride cream and the effects produced by sterilized vaseline in 10 additional patients. In patients who were treated with the 1-percent dyclonine hydrochloride cream, results were good to excellent in 44 patients (88 percent), and little or no effect was observed in 6 patients (12 percent). Of the 25 patients who were treated with known topical anesthetics, good to excellent results were noted in 68 percent (17 patients). The remaining 32 percent (8 patients) received little or no benefit from the known topical anesthetics. Good results were obtained in 2 (20 percent) of the 10 patients treated with sterile vaseline. Little or no effect was observed in the rest of this group (Ref. 5).

Shelmire et al. conducted a study in which patients with various forms of pruritic and painful lesions received topical application of a 1-percent dyclonine hydrochloride cream (Ref. 5). Of a total of 200 patients who received an adequate followup, 113 (56.5 percent) experienced complete relief from pain and/or pruritus, and 31 patients (15.5 percent) received no benefit.

Noojin investigated the effect of a 1-percent dyclonine hydrochloride cream in 335 patients with pruritic dermatoses (Ref. 5). Improvement was observed in 256 patients (76.4 percent), while there was no change observed in 48 patients (14.3 percent). In 31 patients (9.2 percent), the pruritus worsened.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 1.0 percent concentration of dyclonine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Adriani, J., "Absorption and Systemic Toxicity of Local anesthetics," *General Practitioner,* 25:82–86, 1962.

(2) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 467–468, 1973.

(3) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(4) Abreu, B. E., A. B. Richards, L. C. Weaver, G. R. Burch, C. A. Bunde, E. R. Bockstahler, and D. L. Wright, "Pharmacologic Properties of 4-Alkyloxy-Beta-(1-Piperidyl) Propiophenones," *The Journal of Pharmacology and Experimental Therapeutics,* 115:419–426, 1955.

(5) OTC Volume 060025.

(6) Adriani, J. and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:527–530, 1956.

(7) Adriani, J., R. Zepernick, J. Arens, and E. Authement, "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics,* 5:49–62, 1964.

(8) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

m. *Histamine dihydrochloride.* The Panel concludes that histamine dihydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Histamine dihydrochloride ($C_5H_5N_2.2HCl$) is the salt of the histamine base. Histamine is partly responsible for the actions of aqueous extracts of ergot, and was formerly named ergamine and ergotidine. It is found in many tisses, generally in the inert form. It is derived from histadine by the loss of the carboxyl from the amido groups, by bacterial action in the intestines, and by putrefaction (Refs. 1 and 2).

(1) *Safety.* Clinical use has confirmed that histamine dihydrochloride is safe in the dosage range used as an OTC external analgesic.

Marketing data support the safety of histamine dihydrochloride. One manufacturer reported sales of more than 22,300,000 units between 1960 and 1972, with 6 complaints in 1971 and 10 complaints in 1972 (Ref. 3). A second manufacturer has averaged more than 500,000 trade packages per year, with an average of 2 to 4 complaints per year (Ref. 4).

Histamine is present and bound in some inactive form in most tissues of the body, notably the lungs, mast cells, and leukocytes (Ref. 5). When administered by mouth it has little effect because it is destroyed in the digestive tract, but when it is injected subcutaneously or intravenously it produces intense direct stimulation of the tonus or rhythm of smooth muscle (Ref. 2). The acute toxicity differs considerably among various species and circumstances. Mice show a high resistance to histamine toxicity with an LD_{50} of 2.5 g/kg after intraperitoneal injection. Their resistance appears connected with the adrenal medulla. Excision of the adrenals increases the toxicity a hundred times to 0.025 g/kg (Ref. 2).

The systemic effects of histamine dihydrochloride are increases in heart rate, cardiac output, pulmonary ventilation, and metabolic rate (Ref. 6). As the concentration increases, there is a decrease in blood pressure, a feeling of generalized flushing and warmth about the head and neck, and sometimes headache. Overdosage with histamine is rare and symptoms are commonly, if not always, more alarming than dangerous (Ref. 7). The topical effects are similar to topical heat application (Ref. 8). There is vasodilation. The response suggests mediation by a nerve-conducting mechanism.

Shelley and Melton (Ref. 9) observed that penetration of histamine base through intact skin was accelerated by increasing the concentration of histamine in the vehicle, using histamine in the form of the base and a suitable liquid vehicle. The skin is permeable to the base and impermeable to the salt (Ref. 9). The slightest break in the integrity of the skin led to a very rapid penetration of histamine. No systemic manifestations of histamine toxicity were noted in this study (Ref. 9).

Kling (Ref. 10) in 1934 demonstrated pronounced effects on the peripheral circulation when a 1:100 histamine solution infiltrated skin through a needle prick or was applied to a scratch on the skin's surface. The disadvantage of using this technique was that the scratches persisted for about 1 week.

Hummon has used histamine dihydrochloride, in the form of a 1:1,000 solution or a 1-percent ointment, in the administration of histamine by ion transfer (Ref. 6). Hummon stated, "In all our experience with histamine ion transfer we have observed 8 unfavorable reactions, none of them severe, the patients usually complaining of a fullness and throbbing in the head and headache. All of the patients had histamine ion transfer without difficulty at other times, either before or after the unfavorable reaction" (Ref. 6).

The Panel does not question the safety of using low concentrations of histamine dihydrochloride (0.025 to 0.10 percent) for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of histamine dihydrochloride as an OTC external analgesic.

To be effective as a counterirritant, histamine dihydrochloride must penetrate healthy intact skin. Histamine was first administered percutaneously by iontophoresis to produce local dilation of blood vessels (Ref. 11). Kling found that vigorous massage was required in order to cause percutaneous absorption of histamine from an ointment vehicle containing other medical agents (Ref. 12).

Fulton el al. applied histamine to the cheek pouch of hamsters and observed increased circulation produced through dilation of small arterioles (Ref. 8). Shelley and Melton found aqueous vehicles superior to ointments for percutaneous administration of histamine. Application of histamine at the 1-percent level to the intact skin of human subjects showed marked subject-to-subject variation, while 0.1 percent solution of histamine salt or base was generally ineffective. They noted that the slightest break in skin integrity led to very rapid penetration of histamine (Ref. 9).

A report published in 1953 states that the penetration of histamine through the skin is greatly enhanced by topical inunction of a histamine-containing product which also contains methyl nicotinate (Ref. 4). In the report it is postulated that the methyl nicotinate "opened the door" of the skin to the histamine. However, the Panel finds no additional evidence to support the theory that methyl nicotinate may serve as a vector to promote the percutaneous absorption of histamine salts (Ref. 13).

Selle (Ref. 14) reported that the application of histamine dihydrochloride by iontophoresis during physical therapy resulted in vasodilitation and caused an increase of blood flow in the area and a resultant increase in temperature. Histamine dihydrochloride and not the base is used when the administration of histamine is desired. Histamine dihydrochloride, in an aqueous solution or ointment, hydrolyzes into histamine ion, hydrogen ion, and chloride ion. The administration of histamine by ion transfer has been used by Hummon in the treatment of the various forms of arthritis and peripheral vascular diseases (Ref. 6). Hummon observed that in patients with acute traumatic and post-traumatic conditions treatment by histamine ion transfer resulted in improvements equal to or better than those obtained with heat, massage, and exercise.

Histamine has been used to relieve myalgia. Two methods of application of histamine have been used in conjunction with iontophoresis. In one method, a gauze pad was connected to the positive pole of the apparatus and moistened with a 1:5000 solution of histamine. Then a current of 5 to 15 milliamperes was applied for 5 to 30 minutes. The second method consisted of applying a 2-percent histamine ointment to the skin under an anode. The anode consisted of a gauze pad moistened with isotonic sodium chloride solution. A current of 5

to 15 milliamperes was again applied for 5 to 30 minutes. (Ref. 14).

Histamine dihydrochloride has been effectively used as a topical counterirritant in concentrations of 0.025 to 0.10 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.025 to 0.10 percent concentration of histamine dihydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B. 1 above—Category I Labeling.

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 583–585, 1973.

(2) Sollmann, T., "A Manual of Pharmacology and Its Application To Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 538–540, 1957.

(3) OTC Volume 060033.

(4) OTC Volume 060077.

(5) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1056, 1975.

(6) Hummon, I. F., "Histamine Ion Transfer: A Five Year Evaluation," *Archives of Physical Therapy,* 25:212–216, 1944.

(7) Goodson, W., D. Hahn, T. Hunt, and D. Y. K. Leung, "Augmentation of Some Aspects of Wound Healing by a 'Skin Respiratory Factor,' " *Journal of Surgical Research,* 21:125–129, 1976.

(8) Fulton, G. P., G. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *The Journal of Investigative Dermatology,* 33:317–325, 1959.

(9) Shelly, W. B. and F. M. Melton, "Factors Accelerating the Penetration of Histamine through Normal Intact Human Skin," *Journal of Investigative Dermatology,* 13:61–71, 1949.

(10) Kling, D. H., "Histamine Therapy of Rheumatic Affections and Disturbances of the Peripheral Circulation," *Annals of Surgery,* 99:568–576, 1934.

(11) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 649, 1955.

(12) Kling, David H., "A Histamine Ointment for Cataphoresis and Inunction in Rheumatic Affections and Diseases of the Peripheral Circulation," *Medical Record,* p. 291, 1939.

(13) Freeman, G. R., "DMSO in Otology," *Laryngoscope,* 86:921–929, 1976.

(14) Selle, W. A., "Histamine—Its Physiological, Pharmacological and Clinical Significance," *Texas Reports on Biology and Medicine,* 4:138, 1947.

n. *Hydrocortisone preparations (hydrocortisone, hydrocortisone acetate).* The Panel concludes that hydrocortisone and hydrocortisone acetate are safe and effective for use as OTC antipruritics as specified in the dosage section below. The ingredients depress cutaneous sensory receptors and should bear the labeling for topical antipruritics set forth below.

Hydrocortisone is a naturally occurring steroid found in the adrenal cortex. It is cortisone in which the ketone group on carbon 11 has been converted to a hydroxyl group by the addition of two hydrogen atoms. It is also known as cortisol.

Hydrocortisone is a white powder that is very slightly soluble in water, chloroform, or ether, but is soluble in alcohol. Hydrocortisone is also available as the acetate, which is likewise insoluble in water, and as the phosphate, sodium phosphate, and sodium succinate, which are freely soluble in water.

Hydrocortisone has been marketed in the United States since 1952 as a prescription drug. An effort to change this status was attempted 4 years after its introduction. From August 15 to 17, 1956, FDA held open hearings in Washington, D.C. to examine a petition request for possible transfer of hydrocortisone and hydrocortisone acetate from prescription to OTC status for preparations intended for topical use.

Major discussion centered around three questions: (1) Are ointments and lotions containing not more than 2.5 percent hydrocortisone or hydrocortisone acetate safe for use without a prescription when they are applied to the skin not more than twice daily for not more than 5 days, for the relief of itching and inflammation associated with minor skin irritations? (2) Are ointments or lotions of hydrocortisone or hydrocortisone acetate safe for use without prescription under other conditions of composition and/or labeling? Is a warning against use of such preparations in the presence of infection necessary for safe use without a prescription when the hydrocortisone or hydrocortisone acetate is combined with antibiotic drugs such as oxytetracycline hydrochloride or neomycin sulfate?

Based on this hearing, the Commissioner of Food and Drugs, in a statement published in the **Federal Register** of January 17, 1957 (22 FR 353), denied the proposed exemption of hydrocortisone and hydrocortisone acetate from current prescription status. The resulting action was based on a failure to show safety for self-medication and a need for more testing for percutaneous absorption.

In the **Federal Register** of April 28, 1971 (36 FR 7982), FDA listed the pre-1962 topical corticosteroid products recognized as safe and effective. The listing was a result of a review by the National Research Council of the National Academy of Sciences, which had been submitted a short time before. This document stated that 0.5, 1.0, and 2.0 percent hydrocortisone products in different types of vehicles are generally recognized as safe and effective. It was thus established that FDA recognizes that topical hydrocortisone in concentrations of 0.5 to 2.0 percent is safe and effective for steroid-responsive dermatoses when the drug is used as directed as a prescription drug.

(1) *Safety.* Clinical use as a prescription drug has confirmed that hydrocortisone and hydrocortisone acetate are safe in the dosage range recommended by the Panel for use as OTC external analgesics.

(i) *Animal safety data.* The acute oral LD_{50} of hydrocortisone was found to be 1,800±520 mg/kg in male mice, 800±150 mg/kg in female mice, more than 6 g/kg in rats, approximately 175 mg/kg in guinea pigs, and approximately 400 mg/kg in cats (Ref. 1).

A determination was made by Tonelli as to the acute toxicity of corticosteroids, including hydrocortisone in rats, resulting from single subcutaneous injections of each test material in a vehicle containing 0.5 percent carboxymethyl cellulose, 0.4 percent polysorbate 80, and 0.9 percent sodium chloride (Ref. 2). Five groups of eight rats each were injected with 360, 720, 1,080, 1,440, or 1,800 mg/kg of the hydrocortisone preparation. Deaths did not occur until the seventh day following administration. The median lethal dose was determined to be greater than 1,800 mg/kg at day 7,591 mg/kg at day 14, and 449 mg/kg at day 21. Throughout the study there were no deaths among the rats treated with the vehicle alone. Autopsies of several corticosteroid-treated animals revealed multiple small abscesses in the lungs, kidneys, and/or liver.

To test his hypothesis that the principal causes of death among the test animals were due to supervening infections and generalized septicemia, Tonelli repeated the above study and added 0.1 percent chlortetracycline, a broad-spectrum antibiotic, to the diet of one-half of the test animals. The number of deaths among the hydrocortisone-treated rats receiving the medicated diet was significantly reduced. During the 21-day study, only 4 of 40 hydrocortisone-treated rats receiving the medicated diet died, compared with 29 of 40 hydrocortisone-treated animals receiving the nonmedicated diet. The median lethal dose for the hydrocortisone-treated animals receiving a medicated diet was greater

than 2,400 mg/kg at days 7 and 14 and approximately 2,400 mg/kg at day 21. Tonelli concluded that "Corticosteroid lethality increased with time. The principal cause of death was a generalized septicemia, as evidenced by abscess formation in major organs presumably due to suppression of the animal's immune-response mechanism. Concomitant administration of a broad-spectrum antibiotic reduced the toxicity of four of the five corticosteroids tested." The Panel notes that Tonelli also concluded that hydrocortisone was found, based upon median lethal dose determinations, to be significantly less toxic than any of the six other glucocorticoids (i.e., triamcinolone, triamcinolone acetonide, dexamethasone, prednisolone, 21-deoxytriamcinolone acetonide, and 9 *alpha*, 11 *beta*-dichloro-21-hydroxy-16 *alpha*, 17 *alpha*-(isopropylidenedioxy)-1, 4-pregnadiene-3,20-dione) tested in both of the above studies.

Subacute toxicity studies performed by various investigators viewed the effects of corticosteroids on total body weight loss, and the long-term effects of inhibition or reduction of deoxyribonucleic acid (DNA) synthesis on various body structures including circulating lymphocytes.

Such studies performed by Stevens et al. in adrenalectomized mice supported previous findings that corticosteroids with certain molecular structures "diminish the mass of lymphatic tissue and decrease the number of circulating lymphocytes" apparently "by bringing about destruction and enhancing the maturation and death of lymphocytes as well as inhibiting their proliferation" (Ref. 3). The test animals received intraperitoneal injections of 1 mg hydrocortisone acetate in 0.25 mL 0.9 percent saline, and then received injections of 1 microcurie thymidine-2-^{14}C at various times before being sacrificed 30 minutes after the later injection. The time intervals studied ranged from 7 to 360 minutes after the administration of the hydrocortisone acetate preparation. There was a significant decrease in the weight of the spleen per 100 g of body weight after 120 and 360 minutes and in the weight of the thymus per 100 g of body weight after 360 minutes. Neither the spleen, thymus, nor lymph nodes showed a significant change in the total amount of DNA or ribonucleic acid (RNA) apparently "due to the phagocytosis of nuclear and cytoplasmic debris by macrophages and preferential loss of other cytoplasmic constituents." The lymph nodes and thymi showed a significant decrease in the incorporation of thymidine-2-^{14}C into DNA at 120 minutes and thereafter. Stevens et al. concluded that "whatever other effects corticosteroids have on lymphocytes, they do inhibit the synthesis of DNA as measured by the incorporation of thymidine-2-^{14}C." According to Stevens et al., two factors may be responsible for the inhibition of DNA synthesis in the thymi and lymph nodes produced by hydrocortisone: a destructive effect of the hormone on the lymphocytes and the effect of the hormone on metabolic processes in such cells, the result of which is a decrease in DNA synthesis.

Ingle et al. demonstrated the quantitative differences in the biologic properties of corticosterone and its oxygenated derivative, hydrocortisone (Ref. 4). Subcutaneous injections of various amounts (0.5 to 5.0 mg daily) of each compound in a sesame oil vehicle (0.5 mL per injection) were administered in divided daily doses to 5 infection-free male rats immediately following force feedings of a high carbohydrate diet. At the 5-mg daily dose, glycosuria with hyperglycemia was induced in 80 percent of the test animals receiving hydrocortisone (maximum glycosuria value of more than 9 g of gulcose daily) as opposed to 40 percent of those receiving corticosterone (maximum glycosuria value of over 2 g daily). At this daily dosage level, hydrocortisone produced a more marked loss of body weight and a greater increase in the excretion of sodium, chloride, potassium, and nitrogen. At lower daily doses, hydrocortisone, but not corticosterone, produced a temporary increase in sodium, chloride, and nitrogen excretion and caused a definite loss of body weight.

As a followup to published reports that glucocorticoids inhibit mitosis and have been demonstrated autoradiographically to inhibit the healing of gastric ulcer and regeneration of the liver after partial hepatectomy, Lahtiharju et al. (Ref. 5) conducted an autoradiographic study comparing the effect of a single corticosteroid dose on DNA synthesis of cells of the stomach and other organs in white male mice. The abdominal cavities of the test animals were injected with single doses of 1.0 mg hydrocortisone or 0.05, 0.1, or 0.5 mg dexamethasone followed by an injection of 1 microcurie per gram (μC/g) of ^{3}H-thymidine 5 hours later. Control animals initially received injections of physiological saline. The animals were decapitated 1 hour after receiving the ^{3}H-thymidine injection. Autoradiograms of tissue samples were prepared, and the percent ratio (thymidine index) of the labeled cells was counted. After a single does of either of the two corticosteroids, "a significant decrease in DNA synthesis was established autoradiographically in the epithelial cells of the mouse stomach and a slight decrease was established in the duodenal cells and the cells of the liver mesenchyma." The investigators observed that the corticosteroid-treated mice showed no evidence of hepatocyte inhibition.

Ingle and Meeks studied the biologic effects of continuous subcutaneous injections of hydrocortisone and cortisone in normal male rats force-fed a medium carbohydrate diet (Ref. 6). Aqueous solutions of 1, 2, or 4 mg of each corticosteroid in 5 percent ethanol and 0.9 percent sodium chloride were administered by continuous subcutaneous injection for 10 days. The third load remained constant at 20 mL/rat/day. The investigators reported that "the indices of hypercorticalism were weight loss, negative nitrogen balance, glycosuria, atrophy of the adrenal cortex and of the thymus, and gross pathologic changes, such as renal damage and stomach ulcers. The extent of response was related to the dose of each steroid. The quantitative activity of hydrocortisone was approximately twice that of cortisone as indicated by each of the several indices of hypercorticalism."

Investigation into the safety of hydrocortisone use on healing tissues has also been reviewed by the Panel. Reynolds and Buxton observed aberrations produced by exogenously administered hydrocortisone in healing regenerative tissue of male albino rats (Ref. 7). The test animals were wounded by excising a 2-cm circle of skin, extending to, but not including, underlying fascia, from the shaved dorsum of each animal. On the fifth postwounding day, 15 test animals received intramuscular injections of 25 mg/kg hydrocortisone daily for 6 days. The investigators reported that "administration of exogenous hydrocortisone inhibits contraction of open skin wounds, with lysis of cell components and increasing both protein and non-protein nitrogen components, but particularly the non-protein fraction." The large amounts of non-protein nitrogen fragments suggested, and microscopic examination confirmed, a reduction in fibril formation, and high glutamic oxalacetic transaminase (GOT) concentrations indicated a sustained cell destruction which was also confirmed by microscopic examination. A simultaneous accumulation of sialic acids indicated a continuing polysaccharide matrix. A hypocellular

and hypofibrillar wound with delayed contraction and little tensile strength thus resulted.

Vogel studied the effects of corticosteroids on wound tensile strength in male rats when the corticosteroids were administered at various phases in the wound-healing process (Ref. 8). An incision approximately 3 cm long was made down to the fascia in the shaved dorso-lumbar region of each test animal. The test animals received daily subcutaneous injections of 5 or 50 mg/kg hydrocortisone and were sacrificed on days 3, 6, 9, 12, or 20 following wounding. Wound tensile strength was decreased between days 3 and 9 in direct proportion to the dose administered, with the greatest decrease occurring on day 6. Vogel reported the following:

On the 12th day and even more distinctly on the 20th day after operation, a reversal of this effect could be observed. Low doses of glucocorticoids resulted in an increase in wound tensile strength, whereas high doses, already toxic after prolonged administration, still caused a decrease. If treatment was started at the end of the collagen phase (11th day), only an increase in wound tensile strength was seen, regardless of the dose of glucocorticoid administered. Short-term treatment during the scar phase (day 19 to 20) resulted in an increase in wound tensile strength which correlated with the dose and potency of the glucocorticoid given. It is therefore concluded that scar tissue of wounded skin reacts like normal connective tissue as far as the increase in tensile strength induced by glucocorticoids is concerned.

Corticosteroids can alter the functions of various enzymes and hormones in the body, as shown by various studies of these effects and their relation to the organ system. Pomerantz and Chuang found that subcutaneous injections of hydrocortisone in hamsters resulted in a decrease in tyrosinase activity which could be prevented by concurrent administration of B-melanocyte stimulating hormone (MSH) (Ref. 9). The investigators reported that hydrocortisone may lower tyrosinase by blocking the release of endogenous MSH and that "it seems likely that conditions in man and other mammals that result in elevated levels of MSH are associated with increases in skin tyrosinase and that the increased enzyme produces the dark skin or hair pigmentation."

Hall and Hall administered 0.5 mg of the water-soluble phosphate form of hydrocortisone twice daily by subcutaneous injection to nine female Holtzman strain rats for 21 days. Then one test animal was sacrified. No appreciable thymic or adrenal atrophy was evident in this test animal at necroscopy, and none of the remaining animals showed significant growth retardation. One mg of a microcrystalline acetate suspension of hydrocortisone was administered once daily by subcutaneous injection to the eight remaining test animals. All animals were sacrificed on day 51 of the study. The investigators reported that inhibition of growth rate was slight during the first 11 days when the phosphate ester of hydrocortisone was administered but became pronounced when the acetate form was substituted (Ref. 10). Macroscopic examination at the time of autopsy showed marked adrenal and thymic atrophy and hypertrophy of the preputial glands. Histologic examination revealed no evidence of cardiac pathology, although the glomeruli of the kidneys "showed intense and irregular capillary dilatation with hypertrophy of the visceral lamina of Bowman's capsule, and the presence of the same curious vesicular structures as have been found to result from cortisone overdosage."

A number of the published studies reviewed by the Panel discuss effects of various doses of corticosteroids on both thymolytic activity and permeability changes in the vascular systems of the body. The systemic anti-inflammatory activities as measured by thymolytic activity of hydrocortisone, betamethasone, and six commercially available topical steroid preparations (i.e, 0.1 percent betamethasone valerate lotion, 0.025 percent fluocinolone acetonide lotion, 0.1 percent triamcinolone acetonide lotion, 0.05 percent flurandrenolone cream, 0.1 percent fluperolone acetate ointment, and 0.02 percent flumethasone pivalate lotion) were compared by Child et al. in intact male and female weanling WAG strain albino rats and female ICI mice. The results were comparable to their topical vasoconstrictor activity in healthy human subjects (Ref. 11). The steroids were injected subcutaneously into the test animals twice daily for 2 successive days, and the thymus glands were removed and weighed on day 3. The relative potency of each steroid was calculated using as metameters the logarithm of the dose and the thymus weight (mice) or the square root of the thymus weight (rats) with covariance corrected for initial body weight. Using the vasoconstrictor test described by McKenzie and Atkinson (Ref. 12), Child et al. applied serial dilutions of each steroid to the flexor surfaces of both forearms of male and female human subjects. After 16 hours the occulsive dressings were removed and the forearms were examined for vasoconstricted patches. Hydrocortisone was found to be the least active, both topically and systemically, among all the steroids tested. Except for betamethasone and betamethasone valerate, there was close correlation betwen the topical and systemic activity rankings of each steroid within the group. The topical activity of hydrocortisone was calculated to be less than 0.1 based on a value of 100 established for fluocinolone acetonide. Hydrocortisone ranked sixth in the group in terms of topical activity. It is important to note that Child et al. concluded, "Although comparison of activity in animals and man is limited by species variation and route of administration, the agreement shown between the ranking orders of topical and systemic activities suggest that in general they are related."

Weston et al. investigated the cellular effect of hydrocortisone on tuberculin reactions in guinea pigs relative to determining the mechanism by which hydrocortisone suppressed delayed hypersensitivity reactions (Ref. 13). One week after sensitization with complete Freund's adjuvant, tuberculin-sensitized Hartley strain guinea pigs received intraperitoneal injections of 10 mg (0.4 mL) hydrocortisone daily for 4 days. Control animals received daily injections of 0.4 mL intraperitoneal saline for 4 days. The investigators reported that "differential cell counts of biopsy specimens revealed that cortisol treatment resulted in a greater reduction in macrophages than small lymphocytes. This disproportionate reduction in macrophages, viewed from the migration inhibitory factor (MIF) model of delayed hypersensitivity, shows that either the sensitized lymphocyte is unable to produce and release MIF or the macrophage itself cannot respond to MIF when treated with cortisol." It was further reported that hydrocortisone therapy consistently resulted in an actual decrease in the diameter of both erythema and induration, and that it significantly reduced the intercellular edema of the epidermis associated with tuberculin skin tests. Retesting three months following hydrocortisone therapy showed the skin tests of the treated and untreated animals were quite similar, thus indicating that the suppressive effect of hydrocortisone was not permanent under the conditions of this study. Weston et al. concluded that the study suggests that hydrocortisone "is exerting its effect on the recruitment or migration of non-

sensitized cells, rather than by eliminating the sensitized lymphocyte itself."

Lykke, Willoughby, and Houck (Ref. 14) studied the effects of hydrocortisone-released protease preparations from rat skin upon the vascular permeability of the rat as a followup to the findings of Houck and Patel (Ref. 15) and Spector (Ref. 16). Houck and Patel observed that, after the injection of hydrocortisone, the extracellular and extrafibrillar compartment of rat skin contains a nonlysosomal, neutral pH optimal proteolytic enzyme that can be inhibited by both soybean trypsin inhibitor and salicylates (Refs. 15 and 17). Spector determined that some proteolytic enzymes are capable of increasing the permeability of the microcirculation (Ref. 16) Hydrocortisone-released protease preparations were prepared from the shaved and cleaned skin of 3 groups of 12 male Sprague-Dawley rats 26 hours after the subcutaneous injection, and 2 hours after the intraperitoneal injection, of 3 mg/kg hydrocortisone. For control purposes, similar preparations were prepared from rats that received injections of the carrier solvent for the above hydrocortisone preparation. Lykke, Willoughby, and Houck (Ref. 14) determined that extracts from the hydrocortisone-treated rats contained a protease, whereas this protease was lacking in extracts from the skin of untreated rats. These investigators reported that intradermal injections of low concentrations of the hydrocortisone-released protease preparation into the shaved abdominal skin of rats resulted in increased vascular permeability and emigration of leukocytes. They concluded, however, that "this protease appears to exert its vascular permeability-enhancing effect by a mechinism that would not seem to rely on the release or activation of many of the well recognized mediators" (i.e., release of histamine and serotonin or formation of vasoactive kinins). According to Lykke et al., a potent permeability factor associated with the systemic treatment of rats with steroids "could well explain the apparent lack of effect of steroids on acute inflammation consisting mainly of increased vascular permeability * * * whereas it is effective against the more chronic type of inflammatory lesion."

Paulsen and Rerup demonstrated that hydrocortisone was capable of penetrating the skin of rats and exerting systemic effects as indicated by involution of the thymus (Ref. 18). One-tenth mL of the acetate or free alcohol form of various concentrations (0.25, 0.5, or 1.0 percent) of hydrocortisone solutions or suspensions in several vehicles (i.e., polyethylene glycol, olive oil, chloroform plus olive oil, physiological saline, or ointment base) was evenly applied once daily for 3 days to the shaved backs of 24- to 28-day-old female rats. Immediately after each application, the treated area was protected by a collar placed around the neck, and the animals were then isolated in glass jars for 2.5 hours. After that time, the shaved areas were washed with acetone to remove possible residues of the hydrocortisone compound. The test animals were sacrificed 72 hours after the first application, and the thymus of each rat was then removed and weighed. The control animals were shaved, handled, and isolated in the same manner as the hydrocortisone-treated animals. The investigators reported that "both the absolute thymus weights and the thymus weights per 10 g of body weight were reduced to less than 30% of those of the control group after cutaneous application of hydrocortisone" and that the difference was highly significant (p = less than 0.001). Paulsen and Rerup could detect no significant difference in results between the various media in which hydrocortisone was dissolved or suspended. A significant dose-response relationship was established once the values were corrected for body weight variance.

In a study conducted by Tonelli, Thibault, and Ringler, the thymolytic activity in rats of various concentrations (250 to 16,000 μg/mL) of hydrocortisone in a 1-percent croton oil vehicle was determined. Each test material was applied topically to the right ear of each of six rats. For control purposes, the vehicle was applied to the right ears of 10 rats. Six hours later both ears of each animal were removed and weighed. Forty-eight hours after application of the above hydrocortisone preparations and vehicle, the test animals were sacrificed, and the thymi were then removed, weighed, and expressed as mg thymus/100 g of body weight. The investigators reported that the effects of the 500 and 1,000 μg/mL concentrations of hydrocortisone on thymus weight were not significant but were highly significant at higher concentrations. They further determined on the basis of radioactivity data that between 22.7 and 28.8 percent of the amount of hydrocortisone applied to the animals' ears was absorbed during the first 6 hours following application (Ref. 19).

The Panel recognizes that demonstration of safety is an essential factor for consideration in topical application of cortisones to the skin. The following animal studies were reviewed by the Panel to observe effects due to systemic absorption or alterations to the skin surface when directly treated.

Baker and Montes noted histochemical changes in the skin of rats following topical applications of a 1-percent hydrocortisone in 25 percent ethanol solution for a period from 61 to 140 days (Ref. 20). Twice daily throughout the study, 0.1 mL of the hydrocortisone solution was applied to an area just caudal to the right ears of 39 Long-Evans rats. The hair in this area was clipped initially and at weekly intervals thereafter. For control purposes, 0.1 mL of the 25-percent ethanol solvent was similarly applied to identical test sites on 39 Long-Evans rats of the same average body weight (314 g). Skin samples were excised from both the treated area on the right side of each animal's neck and from the left, or untreated, side at the termination of the study, with the result that each animal served as its own control. The investigators reported that "treatment with alcohol alone did not modify the skin significantly." They noted, however, that after prolonged local application of hydrocortisone, "Nonspecific esterase was reduced in sebaceous glands. Total DPN diaphorase and lactic dehydrogenase activities were reduced in epidermis coincident with thinning of this structure. These enzymes, in addition to succinic dehydrogenase and cytochrome C oxidase, remained active in the smaller cells of the treated epidermis. Nonspecific esterase, DPN diaphorase, lactic dehydrogenase, and cytochrome C oxidase were depleted from connective tissue cells and the external epithelial sheath of the hair follicle as they underwent involution due to hormone action."

Castor and Baker observed cutaneous modifications resulting from prolonged topical application of various adrenocortical hormones, including hydrocortisone on nontraumatized skin (Ref. 21). Various adrenocortical hormones in a 25-percent alcohol solution were applied daily to the skin of the neck, caudal to the right ear, of 43 adult rats for as long as 180 days. Cortisone and hydrocortisone were administered in daily doses of 25 to 100 mg dissolved in 0.1 mL 25 percent alcohol. Several animals received 0.1 mL daily of a 25-percent alcohol solution of an extract derived from hog adrenal glands which, in terms of liver glycogen units, was equivalent to 1 mg/mL cortisone. For control purposes, 23 test animals received daily applications of

0.1 mL of the 25-percent alcohol solvent. At various times during the study, microscopic examinations were made of biopsies of skin taken from symmetrical areas behind the ears. The investigators summarized their findings as follows:

> The prolonged percutaneous application of adrenocortical hormones modified the histology of the skin, the changes induced being limited to the area of treatment. The epidermis became thinner and, in males, the size of the epidermal cells was reduced. Growth of hair ceased and sebaceous glands became smaller. The thickness of the dermis was reduced, apparently due to loss of substance from the collagenous fibers,the elastic fibers remaining numerous in spite of the treatment. Fibroblasts and other cells of the dermal connective tissue were fewer in number.
>
> The development of a state of refractoriness to the action of the hormones was demonstrated by the resumption in growth of hair in the area of application when treatment was continued for 180 days.

(ii) *Human safety data.* On review of the literature, the Panel found no report on aggravation of cutaneous bacterial, fungal, or virus infection attributable to the topical application of hydrocortisone-containing products (Ref. 22).

A submission reviewed by the Panel made reference to the reports of more than 90 clinical studies, involving more than 12,000 human subjects, that have been published during the first 21 years following the introduction of topical hydrocortisone preparations in 1952 (Ref. 23). Only 222 adverse reactions were reported in these studies. These were all of a minor nature and were primarily attributed to the vehicle or to a contaminant rather than to hydrocortisone. In these studies, hydrocortisone was substantiated as being the causative agent in only 2 of 95 subjects who were treated with topical hydrocortisone preparations and who experienced sensitization or irritation reactions characterized by erythema, desquamation, and itching. In most instances the effects were minor among the 95 subjects who complained of mild itching and burning at the site of application. These effects were attributed to the irritating properties of the vehicle and did not result in discontinuance of treatment. The available literature contains infrequent reports of cases of allergic contact dermatitis from topical hydrocortisone preparations, but in most of these cases patch testing did not demonstrate that hydrocortisone was the sensitizing agent (Ref. 23).

This submission included copies of 19 publications reporting striae formation, atrophy, telangiectasia, and other dermal manifestations which followed topical applications of flourinated steroids and topical applications or systemic use of corticosteroids other than hydrocortisone (Ref. 23). Adam and Craig in 1965 indicated that "no cases of striae formation have been reported with the older steroids, such as hydrocortisone, which suggests that the newer steroids have a more potent effect on dermal connective tissue elements" (Ref. 24).

Hydrocortisone and other steroids are used to treat a variety of dermatologic conditions, especially those accompanied by inflammation. The following set of studies deals with safety considerations concerning histological changes in tissue structure or the possibility of super-infection.

Sneddon noted aggravation and extension of telangiectasia in 14 patients suffering from rosacea and treated by prolonged topical application of flourinated steroids. Termination of treatment in most cases was followed by severe rebound inflammatory changes characterized by edema and acute pustular eruption. Sneddon reported that hydrocortisone, used together with oral tetracycline, did not produce the same effects (Ref. 25). Stevanovic, however, reported corticosteroid-indiced atrophy of the skin with telangiectasia in six patients. One patients was a female who applied a hydrocortisone preparation to the upper eyelids as a cosmetic for several years (Ref. 26). According to Stevanovic, histological examination "suggested that the first changes in the dermal tissue occur in the ground substance, followed by those of elastic and collagen fibers. These changes are ascribed mainly to the incomplete inhibition of fibroblasts by the corticosteroid." Stevanovic indicated that the atrophy with telangiectasia induced by hydrocortisone "can best be explained by its very prolonged used and the special microanatomical features of infected skin."

Goldman, O'Hara, and Baskett reported that 45 biopsies performed on normal skin areas following local intradermal injections of a hydrocortisone acetate suspension produced "hematoxylinophilic masses persistent over a considerable period of time" and that "Preliminary histochemical studies suggest that these are ground substance changes" (Ref. 27). These investigators further reported that 42 biopsies performed on skin with a variety of inflammatory conditions, and following local injection of a hydrocortisone acetate suspension, "revealed definite inhibition of inflammation in the eczematous, toxic (not too severe), tuberculin, psoriatic, sarcoidal, neurodermatitic keloidal, lymphomatous and leukemic skin reactions and also in some miscellaneous disorders." In contrast, "Biopsies of the urticarial reaction and the local histamine wheal have revealed no significant changes." Goldman later reported that "detailed studies, after local application of both ointments and lotions of the hydrocortisone acetate and free alcohol . . . have shown no histopathologic reactions in normal skin" and that "chromatographic and colorimetric assay controls with hydrocortisone acetate and free alcohol also have revealed no evidence of absorption, in spite of definite local clinical responses" (Ref. 28).

In studies conducted by Fleischmajer, two patients treated with prolonged topical applications of a 2.5-percent hydrocortisone ointment for pathologic skin conditions "developed pustular eruptions and crusting, apparently as a result of secondary infection in skin areas affected by severe excoriations from scratching" (Ref. 29). The infection disappeared, however, following local and systemic administration of antibiotics, without any interruption of the topical hydrocortisone treatment. In another study, 708 patients, most of whom suffered from various types of eczema confined to small skin areas, were treated with topical applications of hydrocortisone, in various formulations, as the acetate or free alcohol, and in concentrations ranging from 0.25 to 2.5 percent. The eczematous lesions worsened in 22 cases (approximately 3 percent) following such treatment (Ref. 30). The investigators reported that "sometimes changing to another ointment base was helpful." Patch testing never showed hypersensitivity to hydrocortisone, but occasional intolerance to all available hydrocortisone products has been shown. Its complete failure, in certain cases where a response might be expected, is unexplained. In a few cases, increased infection has occcured, e.g., *Staphylococcus aureus* in seborrhoeic eczema. On the other hand, it was reported that there seems to be little or no evidence that hydrocortisone ointment positively favors superficial infections. More recent double-blind studies conducted by Carpenter et al. (Ref. 31) revealed that topical applications of a 1.0 percent hydrocortisone cream, three times daily, to patients with acute dermatoses (primary diagnosis of contact, eczematoid, or atopic dermatitis, neurodermatitis, or intertriginous eruption, complicated by suspected

secondary bacterial or fungal infections, produced no increase in infection 7 to 10 days after the initiation of treatment. There was a significantly greater overall response of the lesion and symptomatic improvement, compared with patients treated similarily with the base or cream alone. Pathogens were distributed evenly among the two treatment groups, and *Staphylococcus aureus* was the most frequent contaminant. Seven to 10 days following the initiation of treatment, 31 percent (21 of 68 patients) of the hydrocortisone-treated group were pathogen-negative, compared with 27 percent (18 of 68 patients) of the base cream-treated group.

Wachs, Clark, and Hallett (Ref. 32) treated 100 patients suffering from psoriasis, atopic dermatitis, or various eczemas and dermatoses, with topical applications of either betamethasone valerate or fluocinolone acetonide two or three times daily for 3 weeks. Both of these corticosteroids are more potent than hydrocortisone and were applied in a random, double-blind manner without the use of occlusive dressings. The above investigators reported "no change either in the patient's bacterial flora or in the incidence of fungal isolation" and concluded that "it may be that the threat of overgrowth after routine topical treatment does not exist, or has been overemphasized."

A submission reviewed by the Panel referred to eight clinical studies, published between 1954 and 1957, in which some patients experienced irritation or aggravation of their condition after topical applications of hydrocortisone preparations. In almost all instances, the irritation or aggravation subsided with continuing treatment or a change in the hydrocortisone vehicle base (Ref. 23).

The Panel thoroughly reviewed literature concerning the safety of hydrocortisone. Strong emphasis was placed on isolating cases of adverse reactions. According to a submission reviewed by the Panel, only three cases of serious adverse effects from the use of topical hydrocortisone preparations have been documented in the literature between 1952, when such preparations were first introduced, and late 1973, when the submission was prepared (Ref. 23).

In 1962 Fanconi reported a case of an infant with generalized eczema who experienced a temporary retardation of growth while receiving total body inunction with a 1.0-percent hydrocortisone ointment, twice daily for 6 months (Ref. 33).

Benson and Pharoah in 1960 reported a case of a 5½-year-old boy who had suffered from chronic eczema since the age of 6 months and who had been treated with a nongreasy 1-percent hydrocortisone alcohol ointment for 16 months before being hospitalized. He had developed vomiting and coughing that continued for 1 week before hospitalization. The child also experienced bilateral frontal headaches 3 days before treatment was sought (Ref. 34). Upon examination, the subject showed evidence of growth retardation (i.e., 42-inch height was less than third percentile), bilateral papilledema of moderate severity due to benign intracranial hypertension, and accelerated weight gain during topical hydrocortisone treatment. Hydrocortisone treatment was discontinued at the time of hospitalization, and the symptoms disappeared in a few days. The papilledema also disappeared rapidly and the fundi regained their normal appearance within 4 weeks.

Feinblatt et al. in 1966 reported a case of a 3-week-old male infant who received topical applications of 0.25 percent hydrocortisone with tetracycline phosphate complex and amphotericin B in an "acid-mantle lotion," three times daily for a period of 8½ days, for the treatment of epidermolysis bullosa lesions. During that period the infant received a total of 300 mg hydrocortisone or 2,100 mg/m ^{2} of body surface area. By the fourth day of treatment, a rapid gain in body weight was noted; puffy eyelids and pitting edema of the legs were also observed. At that point the use of the lotion was discontinued. Two days later the rapid increase in body weight ceased, but the infant remained edematous for about 1 week (Ref. 35).

In the three cases cited above, the topical applications of hydrocortisone preparations were excessive. The applications were made either for prolonged periods of time or were made over extensive areas of the body. In each case, however, the clinical status of the subject returned to normal following the discontinuance of topical hydrocortisone treatment. The latter two patients cited in the cases above showed abnormal vital signs. The 3-week-old infant experienced rapid breathing, and the 5½-year-old boy had a pulse rate of 90/ minute and a blood pressure of 95/95. Their vital signs, however, returned to normal after topical hydrocortisone treatment was discontinued.

In more than 12,000 subjects treated with topical hydrocortisone and 90 clinical studies and almost 30 experimental or safety studies, no other abnormal vital signs were reported (Ref. 23). These same studies also revealed abnormal laboratory findings for blood chemistry, liver function tests, or routi urinalysis.

During the last 20 years a variety of absorption, excretion, and metabolism studies have been conducted to evalua the extent of percutaneous absorption topically applied hydrocortisone preparations and the systemic effects percutaneous absorption. These studie have established that percutaneous absorption does indeed occur, but that is always at such a low level that it is unlikely to cause systemic effects similar to those that occur following systemic administration of the drug (i.e Collagen degeneration, cutaneous stria formation, osteoporosis, overt diabetes or high blood glucose, hypokalemia, electrocardiographic abnormalities, muscular weakness, detectable psychological abnormalities, peptic ulcer, and supression of the adrenal axis).

In 1956 Scott and Kalz conducted autoradiographic studies of skin biopsies after topical application of a 1 percent radioactive hydrocortisone ointment to the normal skin of the upp back of six subjects. Results suggested that some systemic absorption occurre Autoradiographs of normal skin 1 hour after application of the ointment demonstrated that the readioactive hydrocortisone had been "distributed through the epidermis, with slightly more dense accumulation near the surface. After 2 hours, there was a high concentration of the material in the basal layer of cells. Dispersion of C^{14} was seen to have occurred through the dermis after 6 hours, with apparent collection of the material around the blood vessels; the basal layer still contained a quantity of the isotope however. After 16 hours, little or no radioactive particles remained in the section of skin, suggesting the systemic absorption of the C^{14}" (Ref. 36). These investigators observed that there appeared to be no difference in the course of absorption, whether the preparation remained on the skin 2 hours or 6 hours. They concluded that "once epidermal penetration had occurred, the process of subsequent absorption proceeded without interruption." Their investigation reportedly dispels the hypothesis that the main route of topical hydrocortison absorption is via the hair follicles and the orifices of glands. They noted that there was no more rapid appearance of C^{14} in the skin adjacent to such structures than in the remainder of the skin immediately subjacent to the epidermis on other sites.

Later studies reported by Malkinson in 1958 (Ref. 37) revealed that no significant absorption of hydrocortisone by normal skin occurred 5½ to 6 hours after topical application of a radioactive hydrocortisone ointment to eight sites on the flexor surface of the forearm of four human subjects. Malkinson further reported that there was no evidence of hydrocortisone absorption following application of a radioactive hydrocortisone ointment to normal skin and before and after exposure of the skin sites to an erythema-producing dose of ultraviolet light. When this ointment was applied to a total of five skin sites in three subjects immediately following stripping, gas-flow cell measurements detected evidence of C^{14} absorption at all test sites. There were levels of residual radioactivity ranging from 52 to 84 percent within the first 5 minutes after application. Radioactivity at these sites had decreased to anywhere from 16 to 37 percent of original levels after 1 hour, and to 10 to 22 percent after 4 to 6 hours. Malkinson remarked, however, that it was not surprising to him that penetration of hydrocortisone-4-C^{14} in normal skin was not detected by the gas-flow cell, because the quantitative absorption of this compound "is well within the inherent percentage of error of this device." He had found previously, from detection of radioactivity in urine extracts, that hydrocortisone-4-C^{14} is "absorbed from normal skin in small quantities approximately 1 to 2 percent of the topically applied material" (Ref. 38).

Studies conducted by Greaves demonstrated that there is some in vivo destruction of hydrocortisone (Ref. 39). Hydrocortisone that contained tritium was applied under occlusion to the skin of the abdomen, forehand, and/or scrotum of a normal male and female subject. After 12 hours, less than 0.5 percent of the radioactive hydrocortisone applied to the abdomen was detectable in the urine and occurred predominantly as 17-oxysteroids. Seventeen percent of the radioactive hydrocortisone that was applied to the scrotum was excreted as corticosteroids, with a distribution of metabolites similar to that following oral administration of hydrocortisone. Greaves feels the data suggest that hydrocortisone "When topically applied loses its side chain before reaching its site of action in the cells and so becomes physiologically inactive. The greater potency of triamcinolone and fluocinolone acetonides administered percutaneously may be in part due to the fact that their side chains cannot be cleaved."

Feldmann and Maibach performed studies in which they quantitated the effect of regional variation in normal male subjects on the percutaneous penetration of hydrocortisone (Ref. 40). They reported that absorption is increased in regions with large or numerous hair follicles and is decreased in some regions having thickened stratum corneum. These generalizations, however, do not apply to absorption through the palm of the hand and scrotum. There was significant absorption from the palm of the hand, even though it has a fairly thick stratum corneum and no hair follicles. The scrotum presented almost no barrier to hydrocortisone penetration. Feldmann and Maibach indicated that "other determining factors may be present in these regions of obvious specialization in structure and function." The Maximum C^{14} urinary excretion rate was achieved during the second 12-hour period for all areas except the foot, where the maximum rate was reached on the third and fourth days, and the back, where the maximum rate was reached on the second day. The above investigators reported the following maximum C^{14} urinary excretion rates per 24 hours, in percent of the applied dose of hydrocortisone: 0.32 percent for the ventral part of the forearm, 0.62 percent for the dorsal part of the forearm, 0.04 percent for the plantar foot arch, 0.14 percent for the lateral ankle, 0.29 percent for the palm of the hand, 0.40 percent for the back, 1.74 percent for the scalp; 1.28 percent for the axilla, 5.09 percent for the forehead, 7.84 percent for the jaw angle, and 27.7 percent for the scrotum.

Another study by Feldmann and Maibach (Ref. 41) revealed that "between 0.2 and 1.0 percent of hydrocortisone, applied to normal skin appears in the urine over a period of ten days. Stripping the skin doubles this amount and significantly alters the absorption rate curve. An occlusive dressing increases absorption ten-fold but does not basically alter the absorption rate curve. Evidence is presented suggesting that both the stratum corneum and the Malpighian/basal layers serve as skin barriers."

Percutaneous absorption studies by Feinblatt et al. in normal male children less than 2 years old revealed that an average of 21.6 percent of a hydrocortisone-4-C^{14} cream, applied topically under occlusion to the antecubital fossae, was recovered in the urine within 5 days (Ref. 35). An average of 35.6 percent was recovered under similar conditions from the urine of subjects with atopic eczema, whose ages ranged from 2 months to 18½ years. The recovery rates were highest during the first 2 days after application and declined progressively on subsequent days. The investigators concluded that when hydrocortisone is topically applied under occlusion "a significantly large amount of percutaneous absorption of hydrocortisone occurs through the skin of children. The tendency to use topical steroids indiscriminately must be condemned. When it is required, the amount of drug placed on the skin should be given consideration."

When administered orally or parenterally, hydrocortisone preparations tend to cause a lowering in circulation of eosinophiles. The following studies were performed to determine the extent to which this occurs when the drug is used topically. Thorn et al. in 1948 reported that the intramuscular administration of a single dose of 25 mg purified pituitary adrenocorticotropic hormone to normal subjects and patients with diseases not involving the adrenal cortex consistently produced a marked decrease (approximately 50 percent) in circulating eosinophils within the first 4 hours (Ref. 42).

A study reported by Smith in 1953 (Ref. 43) indicated that "there was no consistent alteration in the circulating eosinophile count after the inunction" of 6 g of a 25-mg/g hydrocortisone acetate ointment on the back, upper arms, and legs of each of eight normal adult subjects. Circulating eosinophile counts were performed the day prior to inunction and at 4, 6, and 28 hours after inunction. Similar results were obtained when the same ointment was applied to the affected areas of seven patients with generalized skin disease. Smith concluded that the data indicate "that there was either no absorption or, at any rate, insufficient absorption to produce a drop in the circulating eosinophile count. It is of course possible that the test used as a criterion of absorption and systemic effect was not sufficiently sensitive to demonstrate blood changes which might result from the absorption of very minute amounts of hydrocortisone. It is however unlikely that the small amounts which would thus escape detection could account for the therapeutic effects reported."

Gemzell, Hard, and Nilzen conducted a study reported in 1954 in which 48 subjects, some of whom were normal and some of whom had very mild mycosis of the feet, a slight dermatitis of the hands, or minor psoriasis plaques,

received a topical application of 200 mg hydrocortisone incorporated into various vehicles. The application was rubbed on the anterior surface of the body from the neck to the knees for 10 minutes (Ref. 44). In all cases the topical application of hydrocortisone was followed by an increase in the plasma levels of 17-hydroxycorticosteroids within 1 hour, but the investigators did not consider this rise to be statistically significant. Two hours after inunction, a decrease ranging from 6 to 34 percent in the circulating eosinophil count was noted. The investigators did not consider this decrease significant because among the control group there was a decrease of approximately 25 percent in the circulating eosinophil count 2 hours after inunction. They indicated, however, that "even if the figures are not statistically significant, they nevertheless suggest a general effect. It is possible that more sensitive methods than those used in this investigation would be necessary to show such an effect. A more sensitive method is not available at present."

The results from an investigation conducted by Fleischmajer and reported in 1961 "strongly suggest that external hydrocortisone treatment does not produce any major systemic effects following the use of large amounts over prolonged periods of time" (Ref. 29). Ten females and 9 males, ranging in age from 5 to 60 years, received topical applications of a 2.5-percent hydrocortisone ointment twice daily over a 3- to 20-month period. The total amount of hydrocortisone applied per subject ranged from 8,750 to 95,000 mg. Fifteen subjects were being treated for atopic dermatitis, one for atopic dermatitis in combination with ichthyosis, and three for lichen simplex chronicus. Three months after initial treatment, the circulating eosinophil count had decreased in 4 subjects, but the count remained unchanged or had increased slightly in the remaining 15 subjects. Other laboratory tests, including a white blood cell differential count, a urinary 17-ketosteroid determination, and quantitative assays of blood glucose and serum electrolytes, were periodically performed. None of these showed any distinct changes.

In the above study conducted by Gemzell, Hard, and Nilzen, five subjects received a subcutaneous injection of 0.5 mg/kg hydrocortisone. It was reported that "the plasma levels of steroids rose in one hour from 13.0 to 19.4 μg per 100 mL of plasma, then fell. The number of eosinophils decreased continuously throughout the 6-hour period and reached the low level of about 50 percent of the initial value." One subject was given 1 mg/kg hydrocortisone in oral tablet form. The investigators reported that for this subject "the plasma level of 17-hydroxycorticosteroids rose in two hours from 17.3 to 69.5 μg, and the eosinophils decreased to zero in the six-hour period" (Ref. 44). These results, according to the investigators, agreed well with previously reported findings on the use of oral hydrocortisone.

Feinblatt et al. in 1966 commented, however, that "depression of eosinophil counts has been accepted in the past as specific evidence of the circulating level of hydrocortisone-like hormones in the blood. In addition to the fact that the amount of hydrocortisone needed to depress eosinophils has not been documented, many investigators have reported on the variability and lability of eosinophil counts and the inadequacy of this method as a means of determining 17-hydroxycorticosteroid levels" (Ref. 35).

The above study by Gemzell et al. (Ref. 44) demonstrated that subcutaneous injection or oral administration of hydrocortisone increases the plasma levels of 17-hydroxycorticosteroids, attaining the maximum levels in 1 to 2 hours. Neither this study nor Fleischmajer's study discussed above (Ref. 29) demonstrated any distinct or significant change in the plasma level of 17-hydroxycorticosteroids or urinary level of 17-ketosteroids following topical application of hydrocortisone.

On the basis that a "suppression of the urinary 17-ketosteroids and an increase in the 17-hydroxycorticosteroids is the expected finding following the systemic administration of hydrocortisone," Smith attempted to show that systemic absorption of topically applied hydrocortisone does occur, by demonstrating an alteration in urinary steroids. He applied 10 g of a 25–mg/g free-alcohol form of hydrocortisone ointment to the back, arms, and thighs of eight normal male adult subjects (Ref. 45). However, Smith found that there was no consistent alteration in the urinary 17-ketosteroids or 17-hydroxycorticosteroids after inunction with the test material, nor was there any significant difference in the above urinary steroid levels following inunction with the ointment base alone. He concluded that "these results indicate that either there was no absorption or there was insufficient absorption to alter these urinary steroids."

A study conducted by Witten, Shapiro, and Silber, reported in 1955, revealed that the "inunction of relative large body areas of normal or diseased skin with 30 g of ointment containing 7 mg hydrocortisone acetate over a 3-day period does not increase the 17,21-dihydroxy-20-ketosteroid levels in urin and blood" (Ref. 46). The study involve six normal adult males, and three females and six males with extensive c generalized skin disease (bullous erythema multiforme, allergic eczematous contact-type dermatitis, pemphigus foliaceus, and psoriasis). Determinations were made immediatel following the collection of urine and blood specimens taken 12 hours after the last topical application of the above hydrocortisone ointment. It was concluded by these investigators that "the findings lend further support to th mass of clinical evidence indicating tha there are no dangers to be anticipated from absorption and consequent systemic effects of therapeutic quantities of hydrocortisone applied topically in ointment form even to large areas of altered skin for long periods of time."

Scoggins and Kliman (Ref. 47) reported the case of a 22-year-old male with psoriasis of 6 years' duration whic had become severe and generalized during the 11 months preceding the study period. Initially, 400 mg hydrocortisone in a cream base was applied daily for 3 days to approximately 20 percent of the body surface. After an intervening control period of at least 9 days, two applications of hydrocortisone with an occlusive dressing, which totalled 1,200 mg hydrocortisone daily, were made to 90 percent of the body surface. The investigators reported that "the smaller dose of hydrocortisone caused a decrease in eosinophil count on the 1st day of treatment and a moderate rise in plasma cortisol concentration. The absorption of small amounts of this dru was difficult to document because the methods used do not permit differentiation between exogenous and endogenous cortisol. The large dose of hydrocortisone produced unmistakable evidence of the presence of exogenous cortisol—that is, a threefold increase in plasma cortisol concentration, marked increases in the steroid content of the urine—and a prompt decrease in eosinophil count." They further reported that "when the large amount of hydrocortisone was applied, sodium excretion was almost completely suppressed, and there was a transient rise in potassium excretion." It was indicated that the amount of 17-hydroxycorticosteroids that is excreted in the urine after daily topical

administration of 1,200 mg hydrocortisone suggests that less than 10 percent of the dose was absorbed. They concluded that without an occlusive dressing, systemically significant amounts of the corticosteroids are absorbed only if the dose applied is very large.

McCorriston (Ref. 48) reported no elevation above normal levels of 17-ketosteroids, creatinine, or corticoids in a 15-year-old female during the 4-week period that the subject applied a 2.5-percent hydrocortisone acetate ointment to her face, neck, both antecubital fossae, and both wrists.

The final concern for safety, highlighted in the remaining studies, deals with prolonged use of steroid products. Questions on steroid accumulation resulting in excess levels in the body, and problems caused by steroid withdrawal are answered based on information appearing in literature over the years.

In "The Pharmacological Basis of Therapeutics," Sayers and Travis reported that administration of large doses of hydrocortisone for prolonged periods "produces changes in carbohydrate and protein metabolism that are, in general, the converse of those in adrenocortical insufficiency. Blood sugar tends to be high, liver glycogen is increased, and there is increased resistance to insulin. The catabolic action of the steroid is reflected in the wasting of tissues, reduced mass of muscle, osteoporosis (reduction in protein matrix of bone followed by calcium loss), and thinning of the skin. In certain instances, a diabetic-like state may be produced" (Ref. 49).

The report in the above study by Scoggins and Kliman involving the 22-year-old male with psoriasis indicated that there was no discernible change in glucose tolerance following the topical application of 1,200 mg hydrocortisone, under an occlusive dressing, to 90 percent of the body surface during a 1-day period. Nor was there a discernible change in glucose tolerance following the daily topical application of 400 mg hydrocortisone, without an occlusive dressing, to 20 percent of the body surface during a 3-day period (Ref. 47).

In the study by Fleischmajer, no definite changes in blood glucose levels could be found in any of the 19 subjects who received topical applications of a 2.5-percent hydrocortisone ointment twice daily over a 3- to 20-month period (Ref. 29).

Munro and Clift (Ref. 50) demonstrated "that patients with chronic skin disease using the quantity of corticosteroid ointments commonly prescribed in general practice and hospital outpatient clinics, are not significantly at risk from adrenal axis suppression." Insulin stress tests were used to determine whether adrenal axis suppression was present in 40 outpatients suffering from eczema or psoriasis and treated with topical corticosteroids for prolonged periods. Thirty-one patients (77.5 percent) had received treament for 3 to 6 years. The subjects applied one or more of the following corticosteroids topically, under occlusion by polyethylene film (50 percent of patients), polyethylene gloves, or coverings over relatively small areas of their skin: 0.1 percent betamethasone 17-valerate ointment (22 patients used this alone), 0.025 percent fluocinolone acetonide, 0.025 percent beclomethasone dipropionate, and small amounts of 1.0 percent hydrocortisone acetate ointment.

The investigators report as follows: "Of the forty patients studied thirty-seven (92.5%) had a normal response on first testing . . . . When the tests were repeated in the three cases with initial abnormal results after 2–5 months with the patients using half their previous dose of topical corticosteroid ointment, all the patients had essentially normal results (one was minimally below the normal range with a maximal level of 19.5 μg/100 mL and an increment of 12 μg/100 mL)." The three patients with abnormal results initially were using 25, 30, and 100 g betamethasone ointment weekly. The first two used polyethylene film occlusion over large areas of their bodies for a 10- and 2-year period, respectively, when their skin disorder was troublesome. The third patient was a small female for whom a weekly dose of 100 g over a 3-year period represented an especially large dose.

Corticosteroids occur naturally in the body. An excess production of corticosteroids or adrenal insufficiency can easily upset homeostatic balance and cause systemic manifestations and alarming symptoms. Possible absorption through the skin of a topically applied hydrocortisone product is an important issue when considering the safety of hydrocortisone in OTC topical antipruritic preparations. The complications of excessive corticosteroids in the body include electrolyte imbalance, hyperglycemia, glucosuria, susceptibility to superinfection due to inhibition of macrophages, and the classical picture of Cushing's syndrome. These characteristics are warnings of systemic buildup.

Numerous tests have been performed on the absorption of topically applied hydrocortisone preparations. Many are reviewed in the preceding section on human safety. Fleischmajer (Ref. 29) applied a 2.5-percent hydrocortisone acetate ointment twice daily to the skin of 19 patients with atopic dermatitis. The study extended over a 3- to 20-month period. The total dose of hydrocortisone applied ranged from 8,750 to 95,000 mg. No characteristic side effects were noted. Seven patients showed some increase in body weight, but there were no changes in eosinophil counts, in white cell differential count, in urinary 17-ketosteroid analysis, or in blood glucose and serum electrolytes values.

Feldmann and Maibach (Ref. 41) noted that following the topical application of C^{14}-hydrocortisone, only 0.2 to 1.0 percent appeared in the urine. The effect of occlusive dressing on the absorption of topically applied corticoids was studied by Feinblatt (Ref. 35). Ten mongoloid subjects with normal skin were treated with C^{14}-hydrocortisone and the treated areas were occluded with polyethylene film. Urinary recovery of hydrocortisone from these subjects averaged 21.6 percent, a 20-fold increase over subjects with nonoccluded areas. However, this difference is not major, and there are no systemic problems associated with it.

The quantity of topically applied hydrocortisone that is absorbed depends upon such factors as the dose of hydrocortisone and the size and location of the area treated (Ref. 40). As stated above, the following percentages represent the amount of C^{14}-hydrocortisone absorbed from various areas of the body: 0.32 percent from the ventral forearm, 0.82 percent from the dorsal forearm, 0.04 percent from plantar foot arch, 0.14 percent from the lateral ankle, 0.29 percent from the palm, 0.40 percent from the back, 1.74 percent from the scalp, 1.28 percent from the axilla, 7.84 percent from the angle of the jaw, and 27.7 percent from the scrotum (Ref. 40). If the ointment is applied to small areas, none of these percentages will reflect a significant increase in systemic corticoid activity. Treatment of a large area, such as the total body area, requires that attention be given to the period of use of the hydrocortisone ointment. Rare systemic effects can occur after prolonged application and when large areas of the body are treated. Only 3 actual cases have been reported during a 21-year period of use of topical hydrocortisone. The changes which occurred were temporary, and the symptoms disappeared when treatment was discontinued (Ref. 23).

Local changes may occur in the skin after long-term application of hydrocortisone, but the incidence is rare and usually results from secondary infection. A change in the type of ointment base used has often caused the

symptoms to regress or disappear (Refs. 29 and 30).

Allergic reactions to cortisone and its derivatives have been reported, but they are rare (Ref. 23). On review of the literature, the Panel found no reports on the aggravation of cutaneous bacterial, fungal, or viral infections attributable to the topical application of hydrocortisone-containing products. Based on the numerous safety studies available and on the long history of topical use, the Panel concludes that hydrocortisone and hydrocortisone acetate are generally recognized as safe for OTC topical use as antipruritics in doses up to 0.5 percent concentration.

(2) *Effectiveness.* There are studies documenting the effectiveness of hydrocortisone and hydrocortisone acetate in the dosage range recommended by the Panel for use as OTC external analgesics.

Hydrocortisone and hydrocortisone acetate are classified as external analgesics because of their effectiveness on the skin as antipruritic agents. Hydrocortisone preparations have had wide usage in the topical treatment of dermatoses and are preferred for topical use over cortisone because they are active on the skin (Ref. 51).

Hydrocortisone and hydrocortisone acetate are two of the most potent and effective agents for the treatment of many common dermatoses. Numerous controlled and uncontrolled studies provide strong documentation for their efficacy as antipruritic and anti-inflammatory agents in the 0.5 to 5 percent dosage range (Ref. 52). In recent years newer studies have investigated the topical use of concentrations in the dosage range of 0.1 to 0.25 percent.

The following table summarizes the studies that are relevant to the topical use of hydrocortisone preparations:

Controlled Studies Demonstrating Effectiveness of Topical Hydrocortisone

Investigator	Disease state	Dosage (percent)	Evaluation
Becker (Ref. 53)	Pruritus ani/vulvae	1.0	89% of patients showed improvement.
Bisley (Ref. 54)	Pruritus ani/vulvae, eczema	1.0	80% of patients had symptomatic relief.
Boffa (Ref. 55)	Eczema, psoriasis lichen planus, various dermatoses.	1.0	90% showed relief.
Carpenter et al. (Ref. 31)	Common dermatoses with secondary bacterial or fungal infections.	1.0	Average of 73.5% of patients improved in all states.
Carter et al. (Ref. 56)	Seborrheic eczema	1.0	74% of patients fast relief.
Clyman (Ref. 57)	Various dermatoses	1.0	Improvement not too significant.
Clyman (Ref. 58)	Eczema, lichen simplex chronicus, dermatosis.	0.5	Showed effective in 70% of cases.
Eskind (Ref. 59)	Contact dermatitis	0.2 to 2.5	Some improvement, especially at the high dosage.
Fisher (Ref. 60)	Lichen planus	1.0	40% effective, but no improvement with control at all.
Frank (Ref. 61)	Various pruritic dermatoses	0.25	Effective antipruritic.
Frank et al. (Ref. 62)	Various dermatoses	0.5 to 1.0	Both dosages showed effectiveness.
Goltz (Ref. 63)	Various dermatoses	1.0	61% showed fast complete improvement.
Haeger (Ref. 64)	Hypostatic eczema (stasis dermatitis).	1.0	73% improved as compared to placebo control ointment.
Heileson et al. (Ref. 65)	Various dermatoses	1.0	51% more activity than inactive control.
Heileson et al. (Ref. 66)	Eczema	1.0	59% of patients who used it improved.
Hill (Ref. 67)	Eczema	1.0	In 74% of patients strong improvement.
Howell (Ref. 68)	Various dermatoses	1.0	88% of patients improved.
Miller (Ref. 69)	Various dermatoses	1.0	76% of patients improved.
Perlstein (Ref. 70)	Nummular eczema	1.0	98% of patients relieved of pruritus and lesions.
Phillips (Ref. 71)	Various dermatoses	1.0	79.2% of patients had symptomatic improvement.
Polano (Ref. 72)	Pruritus/eczema	1.0	90% of patients showed improvement.
Portnoy (Ref. 73)	Dermatitis/eczema	1.0 to 2.5	64% of patients improved with lower dosage.
Rattner (Ref. 74)	Various dermatoses	0.5 to 1.0	1% better; both dosages effective.
Robinson et al. (Ref. 75)	Various dermatoses	0.5 to 2.5	Less than 1% concentration relatively ineffective.
Robinson et al. (Ref. 76)	Various dermatoses	0.5 to 1.0	34% of patients improved with the low dosage; 67% of patients improved with the 1% concentration.
Robinson et al. (Ref. 76)	Various dermatoses	0.5 to 2.5	Higher percentage (62 to 92%) improvement with oily base than with greaseless base.
Russell et al. (Ref. 77)	Eczema, dermatitis, lichen simplex.	1.0	Ony 38% completely relieved.
St. John's Staff (Ref. 30)	Eczema, dermatitis	1.0	65% showed relief of itching, reduction of inflammation, or complete suppression of physical signs.
Stevens et al. (Ref. 3)	Effectiveness measured by lymphocyte response.	0.5 to 1.0	Both dosage levels are active.
Turell (Ref. 78)	Pruritus ani/vulvae	1.0	32% totally cleared.
Wartzki et al. (Ref. 79)	Pruritus, eczema	1.0	64% showed good improvement.
Way (Ref. 80)	Acne	0.25	85% relieved of irritation, erythema.
Welch et al. (Ref. 81)	Various dermatoses	0.5 to 2.5	0.5% may be less effective in severe acute state otherwise equal effectiveness as the 1.0 and 2.5% ointments.
Wilson et al. (Ref. 82)	Eczema, pruritus	1.0	79% showed good to moderate improvement.
Witten et al. (Ref. 83)	Various pruritis	0.1 to 0.5	0.1% dosage helpful; the higher concentration worked well.
Zelcer (Ref. 84)	Various pruritic dermatoses	0.25	Good effect.
Zelcer (Ref. 85)	Various pruritic dermatoses	0.125	Worked in most cases.

Dosage is an important factor in the determination of therapeutic effectiveness. Hydrocortisone preparations have been marketed in a dosage range of 0.5 to 2.5 percent concentrations. It is the Panel's opinion that OTC products should contain the lowest effective dosages. Data that evaluate the effectiveness at low dosage levels are reviewed below.

Frank implemented a study to compare the effectiveness of hydrocoritsone as an antipruritic agent at concentrations of 0.1 and 0.25 percent. The hydrocortisone was incorporated into two different bases to evaluate the effects of the base media on the various pruritic dermatoses. The use of the 0.25 percent preparations resulted in an improvement in the condition in all cases, and relief from itching was almost immediate. At the 0.1-percent level, results from the test preparations could not be differentiated from those of the control preparations (Ref. 61).

A study by Isaac Zelcer further supports the effectiveness of 0.25 percent concentration of hydrocortisone preparations. In this study, 159 patients were treated with 0.25 percent hydrocortisone acetate ointment. The nature of the skin diseases varied and included eczema, contact dermatitis, atopic eczema, seborrheic eczema, dyshidrosis, lichenification, and pruritus ani and vulvae. In most cases, the treatment successfully relieved symptoms of the various skin diseases. It is important to note that a wider range of skin conditions was reviewed in this study, and that the hydrocortisone acetate ointment was, at times, used as other than an antipruritic agent. Failures occurring in this study were attributed to early discontinuance of treatment (Ref. 84).

Hydrocortisone preparations are frequently used as anti-inflammatory agents. They are prefered to cortisone for two reasons. First, local application of hydrocortisone preparations have a more constant anti-inflammatory effect. Second, hydrocortisone preparatons can be used in lower concentrations than cortisone and still be effective. It is interesting to note that despite hydrocortisone's potency, there are no reports of irritation or senstitivity due to it. Where senstitivity has occurred, it was determined that the ingredients in the base vehicle were the causative agents (Ref. 85).

A study conducted by Welch compared the effectiveness of a wide range of topical hydrocortisone concentrations. As other studies have indicated, hydrocortisone preparations are effective for many dermatoses. This study does point out one important factor. The concentrations studies were

equally effective in most cases, but in the acute phase of most dermatoses or in chronic dermatoses associated with lichenification, doses below 0.5 percent were not always effective (Ref. 81).

Hydrocortisone preparations have been used successfully in the topical treatment of many skin diseases. Hydrocortisone prepartions are safe and effective for mild contact dermatitis, transient atopic dermatitis, mild infantile eczema, uncomplicated status dermatitis, and idiopathic pruritus vulva or ani.

In a study by Witten on the treatment of infantile eczema, hydrocortisone was effective in relieving the condition (Ref.46). Interestingly enough, wide body areas were treated, and there were no problems of super-infection.

Over the past 21 years, numerous studies have reported on the effectiveness of topical hydrocortisone preparations as antipruritic and anti-inflammatory agents. The Panel believes that adequate information has been presented and reviewed to support the conclusion that hydrocortisone and hydrocortisone acetate may be used safely and effectively as OTC external analgesics in short-term therapy within the dosage range specified below.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.25 to 0.5 percent concentration of hydrocortisone or hydrocortisone acetate to affected area 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below-Category I Labeling.) In addition, the Panel recommends the following specific labeling for products containing hydrocortisone and hydrocortisone acetate as external (antipruritic) analgesic active ingreients: *Indication.* "For the temporary relief of minor skin irritations, itching, and rashes due to ecxema, dematitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

References

(1) OTC Volume 060106.

(2) Tonelli, G., "Acute Toxicity of Corticosteroids in the Rat," *Toxicology and Applied Pharmacology,* 8:250–258, 1966.

(3) Stevens, W., C. Colessides, and T. F. Daugherty, "A Time Study on the Effect of Cortisol on the Incorporation of thymidine–2–^{14}C Into Nucleic Acids of Mouse Lymphatic Tissue," *Endocrinology,* 78:600–604, 1966.

(4) Ingle, D. J., R. Sheppard, E. A. Oberle, and M. H. Kuizenga, "A Comparison of the Acute Effects of Corticosterone and 17-Hydroxy-corticosterone on Body Weight and the Urinary Excretion of Sodium, Chloride, Potassium, Nitrogen, and Glucose in the Normal Rat," *Endocrinology,* 39:52–57, 1946.

(5) Lahtiharju, A., T. Rasanen, and H. Tier, "Inhibition of DNA Synthesis in Various Organs of the Mouse Following a Single Corticosteroid Injection," *Growth,* 28:221–224, 1964.

(6) Ingle, D. J. and R. C. Meeks, "Comparison of Some Metabolic and Morphological Effects of Cortisone and Hrdrocortisone Given by Continued Injection to Rats," *American Journal of Physiology,* 170:77–80, 1952.

(7) Reynolds, B. L. and R. W. Buxton, "Aberrations Produced in Healing Regenerating Tissue by Exogenously Administered Testerone, Hydrocortisone, and Methandrostenolone," *The American Surgeon,* 29:859–862, 1963.

(8) Vogel, H. G., "Tensile Strength of Skin Wounds in Rats After Treatment with Corticosteroids," *Acta Endocrinologia,* 64:295–303, 1970.

(9) Pomerantz, S. H. and L. Chuang, "Effects of B–MSH, cortisol and ACHT on Tyrosinase in the Skin of Newborn Hamsters and Mice," *Endocrinology,* 87:302–310, 1970.

(10) Hall, C. E. and O. Hall, "Contrasting Effects of Stress and Cortisol Overdosage in the Rat," *American Journal of Physiology,* 196:946–948, 1958.

(11) Child, K. J., A. F. English, H. G. Gilbert, A. Hewitt, and E. A. Wollett, "Vasoconstrictor and Systemic Activities of Topical Steroids," *Archives of Dermatology,* 97:407–410, 1968.

(12) McKenzie, A. W. and R. M. Atkinson, "Topical Activities of Betamethasone Esters in *Archives of Dermatology,* 89: 741–746, 1964.

(13) Weston, W. L., M. J. Mandel, G. G. Krueger, and H. N. Claman, "Differential Suppressure Effect of Hydrocortisone on Lymphocytes and Mononuclear Macrophages in Delayed Hypersensitivity of Guinea Pigs," *Journal of Investigative Dermatology,* 59:345–348, 1972.

(14) Lykke, A. W. J., D. A. Willoughby, and J. C. Houck, "Effects of Cortisol Released Cutaneous Protease upon the Permeability of the Micro-Circulation," *Journal of Investigative Dermatology,* 48:318–325, 1967.

(15) Houck, J. C. and Y. M. Patel, "Proposed Mode of Action of Corticosteroids on the Connective Tissue," *Nature,* 206:158–160, 1965.

(16) Spector, W. G., "Substance which Affects Capillary Permeability, *Pharmacology Review,* 10:475, 1958.

(17) Houck, J. C. and Y. M. Patel, "Hormone and Drug Released Dermal Protease," *Federal Proceedings,* 25:762, 1966.

(18) Paulsen, F. and C. Rerup, "Penetration of Cortison (Hydrocortisone) through the Skin of Rats," *Acta Pharmacologica et Toxicologica,* 12:187–195, 1956.

(19) Tonelli, G., L. Thibault, and I. Ringler, "A Bio-assay for the Concomitant Assessment of the Antiphlogistic and Thymolytic Activities of Topically Applied Corticoids," *Endocrinology,* 77:625–634, 1965.

(20) Baker, B. L. and L. F. Montes, "Histochemical Changes in the Skin Following Local Application of Cortisol and Prednisolone," *Anatomical Record,* 139:133–143, 1961.

(21) Castor, C. W. and B. L. Baker, "The Local Action of Adrenocortical Steroids on Epidermis and Connective Tissue of the Skin," *Endocrinology,* 47:234–241, 1950.

(22) OTC Volume 060178.

(23) OTC Volume 060098.

(24) Adam, J. E. and G. Craig, "Striae and their Relation to Topical Steroid Therapy," *Canadian Medical Association,* 92:289–291, 1965.

(25) Sneddon, I., "Adverse Effect of Topical Fluorinated Corticosteroids in Rosacia," *British Medical Journal,* 1:671–673, 1969.

(26) Stevanovic, D. V., "Corticosteroid Induced Atrophy of the Skin with Telangiectasia," *British Journal of Dermatology,* 87:548–556, 1972.

(27) Goldman, L., H. O'Hara, and J. Baskett, "A Study of the Local Tissue Reactions in Man to Cortisone and Compound–F," *Journal of Investigative Dermatology,* 20:271–279, 1953.

(28) Goldman, L., "Histological Effects of Hydrocortisone is Skin of Man," *Annals of the New York Academy of Science,* 61:520–523, 1955.

(29) Fleischmajer, R., "The Lack of Systemic Hydrocortisone Effects After Massive and Prolonged External Applications," *Journal of Investigative Dermatology,* 36:11–16, 1961.

(30) Staff of Saint John's Hospital for Diseases of the Skin and the Institute of Dermatology, London, "The Value of Local Hydrocortisone in the Treatment of Skin Diseases," *The Practitioner,* 178:337–341, 1957.

(31) Carpenter, C. L. et al., "Combined Steroid-Antiinfective Topical Therapy in Common Dermatoses: A Double-Blind Multi-Center Study of Iodochlorhydroxyquin-Hydrocortisone in 277 Patients," *Current Therapeutic Research,* 15:650–659, 1973.

(32) Wachs, G., R. Clark, and J. Hallett, "Are Topical Steroid-related Superinfections a Myth?," *Cutis,* 12:256–257, 1973.

(33) Fanconi, G., "Hemmung des Wachstums bei Einem Saugling Durch die zu

Intrusive Anwendung Einer 1 percent Igen Hydrocortisona auf der Haut bei Generalisiertem Ekzem," *Helvetica Acta,* 17:267–268, 1962.

(34) Benson, P. F. and P. O. C. Pharoah, "Benign Intracranial Hypertension due to Adrenal Steroid Therapy," *Guy's Hospital Reports,* 109:212–218, 1960.

(35) Feinblatt, B. I., T. Aceto, G. Beckham, and E. Bruck, "Percutaneous Absorption of Hydrocortisone in Children," *American Journal of Diseases of Children,* 112:218–224, 1966.

(36) Scott, A. and F. Kalz, "The Penetration and Distribution of C^{14}-Hydrocortisone in Human Skin After Its Topical Application," *Journal of Investigative Dermatology,* 26:149–158, 1956.

(37) Malkinson, F. D., "Studies on the Percutaneous Absorption of C^{14} Labeled Steroids By Use of the Gas-Flow Cell," *Journal of Investigative Dermatology,* 31:19–28, 1958.

(38) Malkinson, F. D. and E. H. Ferguson, "Percutaneous Absorption of Hydrocortisone-4-C^{14} in Two Human Subjects," *Journal of Investigative Dermatology,* 25: 281–283, 1955.

(39) Greaves, M. S., "The In-vivo Catabolism of Cortisol by Human Skin, " *Journal of Investigative Dermatology,* 57:100–107, 1971.

(40) Feldmann, R. J. and H. I. Maibach, "Regional Variation in Percutaneous Penetration of ^{14}C Cortisol in Man," *Journal of Investigative Dermatology,* 48:181–183, 1967.

(41) Feldmann, R. J. and H. I. Maibach, "Penetration of ^{14}C Hydrocortisone Through the Normal Skin," *Archives of Dermatology,* 91:661–666, 1965.

(42) Thorn, G. W., P. H. Forsham, F. T. Garnet Prunty, and A. G. Hills, "A Test for Adrenal Cortical Insufficiency," *Journal of the American Medical Association,* 137:1005–1009, 1948.

(43) Smith, C. C., "Eosinophilic Response After Inunction of Hydrocortisone Ointment," *Archives of Dermatology,* 68:50–53, 1953.

(44) Gemzell, C. A., S. Hard, and A. Nilzen, "The Effect of Hydrocortisone Applied Locally to the Skin on the Eosinophil Count and the Plasma Level of 17-Hydrocorticosteroids," *Acta Dermato-Venereologica,* 34:327–33, 1954.

(45) Smith, G. C., "Urinary Excretions of 17-Ketosteroid and 17-hydrocorticosteroids after Inunction of Hydrocortisone Ointment," *Journal of Investigative Dermatology,* 25:67–69, 1955.

(46) Witten, V. H., A. J. Shapiro, and R. H. Silber, "Attempts to Demonstrate Absorption of Hydrocortisone by New Chemical Test Following Inunction Into Human Skin," *Proceedings of the Society for Experimental Biology and Medicine,* 88:419–421, 1955.

(47) Scoggins, R. B. and B. Kliman, "Percutaneous Absorption of Hydrocorticosteroids," *The New England Journal of Medicine,* 273:831–840, 1965.

(48) McCorriston, L. R., "Hydrocortisone (Compound F) Acetate Ointment in Eczema of Infants and Children," *Canadian Medical Association Journal,* 70:59–62, 1954.

(49) Sayers, G. and R. H. Travis, "Adrenocorticotropic Hormone; Adrenocrotical Steroids and Their Synthetic Analogs," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., The MacMillan Co., New York, pp. 885–923, 1970.

(50) Munro, D. D. and D. C. Clift, "Pituitary-Adrenal Function After Prolonged Use of Topical Corticosteroids," *British Journal of Dermatology,* 88:381–385, 1973.

(51) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, pp. 1490–1491, 1975.

(52) OTC Volume 060100.

(53) Becker, G. L., "Recent Advances in the Local Treatment of Perianal Skin Lesions," *American Journal of Surgery,* 88:289–292, 1954.

(54) Bisley, B. L., "Efficacy of Two Topical Hydrocortisone Preparations with Antibacterial," *General Practitioner,* 191:101–102, 1965.

(55) Boffa, P. S., "Topical Corticosteroid Therapy in Low Dosage," *General Practitioner,* 199:105–108, 1967.

(56) Carter, V. H. AND R. O. Noojin, "The Evaluation of Betamethasone-17-valerate as a Topical Agent," *Current Therapeutic Research,* 9:253–255, 1967.

(57) Clyman, S. G., "Comparative Study of Dermatological Ointments: Effectiveness of Tarsteroid-Neomycin Compared with Hydrocortisone Alone," *Industrial Medicine and Surgery,* 27:531–532, 1958.

(58) Clyman, S. G., "Comparative Effects of Hydrocortisone and Hydrocortisone Coal Tar Extract Creams in Cases of Atopic Dermatitis, *"Postgraduate Medicine,* 21:309–313, 1957.

(59) Eskind, I. B. "Treatment of Rhus Dermatitis with Topical Hydrocortisone," *Archives of Dermatology,* 69:410–413, 1954.

(60) Fisher, A. A., "The Topical Use of Hydrocortisone Ointment for Certain Oral Conditions," *New York State Journal of Medicine,* 55:2494–2496, 1955.

(61) Frank, L., "A Study of the Antipruritic Effects of Topical Steroids," *American Medical Association Archives of Dermatology,* 77:443–434, 1958.

(62) Frank, L., C. Stritzler, and J. Kaufman, "Clinial Evaluation of Five-Tenths Per Cent Hydrocortisone Ointment," *Archives of Dermatology,* 71:637, 1955.

(63) Goltz, R. W., "Topical Hydrocortisone in the Treatment of Skin Diseases," *Minnesota Medicine,* 38:404–407, 1955.

(64) Haeger, K., "Betamethasone-17-valerate in Topical Treatment of Hypostatic Leg Eczema," *Angiology,* 20:27–32, 1969.

(65) Heilesen, B., A. Kristjansen, and F. Regmann, "Hydrocortisone in the Therapy of Cutaneous Disease," *Archives of Dermatology,* 70:360–362, 1954.

(66) Heilesen, B., A. A. Kristjansen, and F. Regmann, "Hydrocortisone Ointment in the Treatment of Children with Atopic Dermatitis," *Acta Allergologica,* 8:314–322, 1955.

(67) Hill, L. W., "Hydrocortisone Ointment in the Treatment of Infantile Eczema," *The New England Journal of Medicine,* 252:1038–1039, 1955.

(68) Howell, C. M., "An Evaluation of the Treatment of 259 Cases of Inflammatory Dermatoses with Hydrocortisone Free Alcohol Ointment," *Journal of Allergy,* 27:477–479, 1956.

(69) Miller, C. S., "Clinical Value of Hydrocortisone-Oxytetracycline Topical Ointment," *New York State Journal of Medicine,* 56:2098–2099, 1956.

(70) Perlstein, S. M., "Treatment of Nummular Eczema," *Medical Times,* 86:12 1239, 1958.

(71) Phillips, F. J., "Steroid Ointments in General Dermatological Practice II," *Medi Times,* 91:999–1003, 1963.

(72) Polano, M. K., "The External Use of Hydrocortisone in Skin Diseases," *Acta Dermatovenereologica,* 36:283–290, 1956.

(73) Portnoy, B., "A Comparison Betwee 92-Fluorohydrocortisone and Hydrocortiso in the Topical Treatment of Certain Dermatoses," *British Journal of Dermatolo* 68:303–306, 1956.

(74) Rattner, H., "The Status of Corticosteroid Theraphy in Dermatology," *California Medicine,* 83:331–335, 1955.

(75) Robinson, H. M. and R. C. V. Robins "Treatment of Dermatoses with Local Applications of Hydrocortisone Acetate," *Journal of the American Medical Association,* 155:1213–1216, 1954.

(76) Robinson, H. M., R. C. V. Robinson, and J. F. Strahan, "Indications for Local Hydrocortisone Therapy," *Medical Times,* 83:227–237, 1955.

(77) Russell, B., J. S. Pegum, N. A. Thorne and R. V. Grange, "A Valuation of Hydrocortisone Ointment," *Lancet,* 1:1038–1043, 1955.

(78) Turell, R., Hydrocortisone Therapy I Control of Anogenital Pruritus," *Journal of the American Medical Association,* 158:173 175, 1955.

(79) Wartzki, I. M. and B. R. Entwisle, "Topical Hydrocortisone Therapy in Diseas of the Skin: A Clinical Evaluation," *Medica Journal of Australia,* 1:318–325, 1956.

(80) Way, S. C., "Topical Hydrocortisone Therapy in Acne Rosacia and Acne Vulgaris," *New York State Journal of Medicine,* 57:3463–3465, 1957.

(81) Welsh, A. L. and M. Ede, "Further Observations on Hydrocortisone Ointment Their Rational Use in Dermatology," *Ohio State Medical Journal,* 51:350–352, 1955.

(82) Wilson, H. T. and J. H. Edward, "A Comparison of Glycyrrheinic Acid Hydrocortisone Ointment," *British Journal Dermatology,* 70:452–457, 1958.

(83) Witten, V. H., M. B. Sulzberger, E. H. Zimmerman, and A. J. Sharpiro, "A Therapeutic Assay of Topically Applied 92-Fluorhydrocortisone Acetate in Selected Dermatoses," *Journal of Investigative Dermatology,* 24:1–4, 1955.

(84) Zelcher, I., "La Hidrocortisona en el Tratamiento Local de las Enfermedades de Peil (Hydrocortisone in the Local Treatmen of Diseases of the Skin)," *La Semana Midic* pp. 1206–1211, December, 1954, in OTC Volume 060161.

(85) Zelcer, I., "Cortisona e hidrocortisona local; Estudio comparativo de su activadad en dermatologia (Local cortisone and hydrocortisone; Study comparing their activity in dermatology)," *Orientacion Midica,* pp. 1568–1569, December, 1954, in OTC Volume 060161.

o. *Juniper tar.* The Panel concludes that juniper tar is safe and effective for use as an OTC external analgesic as

specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Juniper tar, also known as oil of cade, Haarlem oil, bili-drops, Holland balsam, silver drops, and silver balsam (Ref. 1), is a dark brown, viscous liquid with a smoky odor and an acrid, slightly aromatic bitter taste. It is a volatile oil derived from the wood of *Juniperus oxycedrus Linne.* It is composed of cadinene along with varying concentrations of phenols, cresols, acetic acid, hydrocarbons, resins, and phenolic bodies. Juniper tar is very slightly soluble in water. One volume is soluble in 9 volumes of alcohol and in 3 volumes of ether. It is also soluble in chloroform, alcohol, glacial acetic acid, turpentine, and petroleum ether. Juniper tar is acid in reaction (Refs. 1 and 2).

The cadinenes are sesquiterpenes occurring in essential oils. Nine possible isomers exist. They are capable of forming dihydrochlorides (Ref. 3).

(1) *Safety.* Clinical use has confirmed that juniper tar is safe in the dosage range used as an OTC external analgesic.

Data on oral toxicity are not available in standard texts. From juniper tar's chemical composition, the Panel concludes that it is unsafe for oral ingestion. Oral ingestion may cause injurious effects on the kidneys (Ref. 4).

(2) *Effectiveness.* Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that juniper tar is effective for use as an OTC external analgesic.

Juniper tar is used chiefly in topical therapy of cutaneous lesions. It is markedly keratolytic. It is effective as an antipruritic for the treatment of psoriasis, eczema, and various dermatoses, largely due to the fact that it consists of a mixture of phenolic derivatives. Juniper tar is indicated for the temporary relief of discomfort of minor skin irritations and itching (Ref. 1). Juniper tar is only used externally.

Juniper tar has been effectively used in concentrations ranging from 1 to 5 percent (Ref. 5).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 to 5 percent concentration of juniper tar to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

4. *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1384, 1955.

(2) OTC Volume 060038.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 691, 1976.

(4) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 647, 1973.

(5) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 721, 1975.

p. *Lidocaine.* The Panel concludes that lidocaine is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Lidocaine is an amide type of topical anesthetic and differs from tetracaine, benzocaine, and butamben, which are esters of aminobenzoic acid. Lidocaine is 2-(diethylamino)-2',6'-acetoxylidide (Ref. 1). It can be considered as an acetamide with one hydrogen atom on the amino group of the amide portion of the compound replaced by a dimethyl aniline group and one hydrogen atom on the terminal carbon atom replaced by a nitrogen atom with two ethyl groups. It is a tertiary amine and is a base that forms salts with acids (Ref. 2).

Lidocaine was synthesized by Lofgren in 1946 in Sweden. Lidocaine base is a white to slightly yellow crystalline powder having a characteristic aromatic odor. It is practically insoluble in water, very soluble in alcohol and chloroform, freely soluble in ether, and dissolves in oils. Lidocaine is more lipophilic than procaine. Lidocaine base melts at between 66° and 69° C. Lidocaine base for use as a topical external analgesic is incorporated in water-miscible ointment bases composed of polyethylene glycol and propylene glycol (Ref. 3).

Lidocaine is highly stable in vitro. It endures 8 hours of boiling with 30 percent hydrochloric acid or lengthy heating with alcohol and potassium hydroxide (Ref. 2). However, it is readily metabolized in the body. Up to 11 percent of the usual doses used for regional anesthetic block in man are recoverable in the urine within 4 hours (Ref. 4).

(1) *Safety.* Clinical use has confirmed that lidocaine is safe in the dosage range used as an OTC external analgesic (Refs. 5, 6, 7, and 8). Lidocaine base is poorly soluble in water but is readily absorbed when applied over extensive denuded areas of skin. If sufficient quantities are absorbed, plasma levels may be attained that result in systemic pharmacological reactions characteristic of the "caine" type drugs which may terminate fatally (Ref. 9). Reactions due to systemic absorption affect the central nervous and the cardiovascular system. Stimulation of the cortex occurs first, followed by depression of both the cerebral cortex and lower centers (Ref. 10). Slow onset of a reaction first causes stimulation followed by depression leading to drowsiness, nervousness, dizziness, blurred vision, nausea, tremors, convulsions, and finally respiratory arrest. When the onset is rapid, central nervous system depression occurs, leading primarily to unconsciousness which may be followed by respiratory arrest (Ref. 9). Myocardial depression and cardiac arrest can occur simultaneously. The fall in blood pressure and intercostal paralysis indicates a potential hazard resulting from high plasma levels (Ref. 11).

Lidocaine is used intravenously in small quantities by physicians for its useful antiarrhythmic activity attributed to an increase of the electrical stimulation threshold of the ventricle during diastole. The antiarrhythmic action is similar to that of procainamide and quinidine but, because of its short duration of action, lidocaine must be given by continuous intravenous infusion if the action is to be sustained. The antiarrhythmic action usually develops within a few minutes and lasts 10 to 20 minutes, following a single intravenous injection of 50 to 100 mg. When it is used intravenously at the rate of 10 to 45 μg/kg of body weight per minute, the antiarhythmic action begins in 10 to 20 minutes. Blood levels of 1.0 to 2.5 μg/mL are required to suppress ventricular arrhythmias. These blood levels may be attained by an intravenous priming dose or by continuous infusion of the drug. Blood levels exceeding 5 μg/mL may prove toxic and cause convulsions and cardiac depression. Constant electrocardiograph monitoring is used to avoid overdosage and toxicity. Manufacturers of lidocaine indicate that its specific indication is to manage ventricular arrhythmias occurring during cardiac manipulation such as cardiac surgery. It is used for life-threatening arrhythmias, particularly those of ventricular origin, which occur with acute myocardial infarction (Refs. 12 and 13).

Approximately 90 percent of a dose of lidocaine is rapidly metabolized by the enzymes in the microsomes of the liver,

and the metabolites are excreted along with 10 percent of the unchanged drug into the urine. Lidocaine is metabolized by several metabolic pathways in the liver. The enzymes involved are oxidases and amidases. Several metabolites have recently been found that cause convulsions. These findings may account for delayed reactions due to cumulative effects. Lidocaine is not hydrolyzed by the plasma cholinesterases as are tetracaine, procaine, and other esters of aminobenzoic acid (Refs. 4 and 10).

Neither lidocaine base nor its salts is irritating to intact or abraded skin (Ref. 14). Despite statements made to the contrary, lidocaine can produce sensitization after repeated applications, as do the other "caine" type drugs. However, the incidence of sensitization is extremely low (Ref. 9). The medical literature reports that the amide type of the "caine" local anesthetics is devoid of sensitizing potential (Ref. 10), but such a statement cannot be supported on either a theoretical or a factual basis. Most soluble drugs can act as haptenes and form antigens that stimulate production of immune bodies of the IgE type that cause allergic reactions in susceptible individuals. Anaphylaxis has been reported after application of lidocaine to the mucous membranes and infiltration. One case of an anaphylactic reaction occurred following application to the skin (Ref. 16). The report does not state whether the quantity, which was said to be minute, was injected intradermally or applied by a patch or scratch test. In another case (Ref. 16), a female patient who alleged she was allergic to lidocaine was tested for lidocaine allergy by instilling one drop into the conjunctival sac. The patient developed immediate syncope, circulatory collapse, and then severe shock. Upon treatment with vasopressor agents, antihistamines, and steroids, she recovered after 2 hours.

(2) *Effectiveness.* There are studies documenting the effectiveness of lidocaine as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that lidocaine is effective for use as an OTC external analgesic (Ref. 7).

Lidocaine is widely and effectively used as a topical anesthetic on the mucous membranes in concentrations ranging from 1.0 to 4.0 percent (Ref. 15). Lidocaine is approximately twice as potent and toxic as procaine on a weight basis (Ref. 9). The onset of anesthesia is rapid after injection, requiring less than one minute. The onset of action when the ingredient is used on the skin has not been reported. The Panel concludes that this is variable and difficult to establish, because it will depend upon the degree of penetration and the type of lesion. The base is poorly soluble in water but soluble in lipid substances, glycols, and similar types of solvents. The base penetrates the intact skin and exerts an analgesic and antipruritic action in the skin (Ref. 14).

Lidocaine base is an effective topical anesthetic on the skin and mucous membranes. When properly formulated to ensure its stability and continuous contact with a cutaneous or mucous surface, it provides prolonged analgesia and anesthesia. When incorporated into a vehicle that is sufficiently alkaline to release bioactive quantities of the free base, it penetrates both intact and damaged skin (Ref. 14). Percutaneous absorption occurs, but when lidocaine is applied to limited areas of the skin, blood levels are insignificant and systemic reactions do not occur (Ref. 11). The Panel stresses, however, that no preparation should be applied over a wide area. Lidocaine, like other topical anesthetics of the "caine" type, relieves pain entirely within the skin or in the mucous membranes. The quantity circulating in the blood does not provide analgesia or anesthesia to parts of the body distal to the site of application or in structures beneath skin, such as the muscles, tendons, or joints. Lidocaine blocks transmission at nerve endings by stabilizing the neuronal membrane as do other topical anesthetics of the "caine" type (Ref. 2). Dalili and Adriani (Ref. 14) found that a 1-percent solution of the lidocaine hydrochloride did not block the effects of electrical stimulation on receptors eliciting sensation of burning and itch. When the skin was burned with ultraviolet light, the application of the solution of lidocaine hydrochloride exaggerated, rather than relieved, the pain. They were able to obtain blockade of the sensation of pain and itch using a saturated solution of lidocaine base in a solution composed of 40 percent alcohol, 10 percent glycerin, and water. Anesthesia, which began to diminish after 4 hours had elapsed, persisted as long as the film of the preparation remained in contact with the skin.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 4 percent concentration of lidocaine to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesth and antipruritic active ingredients. (part III. paragraph B.1. below—Cate I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in la quantities, particularly over raw surfaces or blistered areas."

References

(1) Windholz, M., "The Merck Index," Ed., Merck and Co., Rahway, NJ, p. 717, 1

(2) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(3) Osol, A. and R. Pratt, "The Dispens of the United States," 27th Ed., J. B. Lippi Co., Philadelphia, p. 667, 1973.

(4) Adriani, J. and M. Naraghi, "Pharmacologic Basis of Regional Pain Relief," *Annual Review of Pharmacology Toxicology,* 17:223–242, 1977.

(5) OTC Volume 060020.

(6) OTC Volume 060043.

(7) OTC Volume 060049.

(8) OTC Volume 060071.

(9) Adriani, J., "Absorption and Systemi Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(10) Covino, B. G., "Local Anesthesia," *England Medical Journal,* 286:975–983, 197

(11) Adriani, J. and D. Campbell, "Fatali Following Topical Application of Local Anesthetics to Mucous Membranes," *Jour of the American Medical Association,* 162:527–530, 1956.

(12) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5 Ed., Macmillan Publishing Co., Inc., New York, pp. 696–697, 1975.

(13) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 13–18, 1977.

(14) Adriani, J. and H. Dalili, "Penetratio of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:83 841, 1971.

(15) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 277–279, 1977.

(16) Adriani, J., Personal communication.

q. *Lidocaine hydrochloride.* The Pan concludes that lidocaine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruriti set forth below.

Lidocaine hydrochloride is the salt of lidocaine base, a tertiary amine. The chemistry of lidocaine base has been described elsewhere in this document. (See part III. paragraph B.1.p. above—Lidocaine.) Lidocaine hydrochloride is a white crystalline powder with a slightly bitter taste. It melts at between 74° and 79° C. It is very soluble in water, alcohol, and chloroform, but is insoluble in ether (Ref. 1). Lidocaine hydrochloride is very stable in vitro and

withstands boiling in 30 percent hydrochloric acid for 8 hours or more. Aqueous solutions are acid in reaction, the pH ranging from 5 to 6.4 (Ref. 2). The salt is highly ionized and not lipophilic. When injected into the tissues, it is converted to the free base due to the buffering mechanisms present in the tissues. The free base is the physiologically active form. The nitrogen atom on the cation of lidocaine hydrochloride is converted from a tertiary one to a quaternary (Ref. 3).

(1) *Safety.* Clinical use has confirmed that lidocaine hydrochloride is safe in the dosage range used as an OTC external analgesic.

The general properties and chemistry of lidocaine have been described elsewhere in this document. (See part III. paragraph B.1.p. above—Lidocaine.) Lidocaine hydrochloride is very soluble in water. It is twice as potent and twice as toxic as procaine. It is readily absorbed from open lesions when the stratum corneum has been removed and deeper layers of the skin exposed. Absorption is followed by significantly perceptible blood levels that result in systematic toxicity if lidocaine hydrochloride is applied to extensive areas. Human toxicity varies with individual tolerance, age, sex, health, and tissue vascularity. Convulsions and cardiac depression may occur if the drug is applied over extensive abraded areas (Refs. 4 and 5). However, systemic toxicity has not been demonstrated when lidocaine hydrochloride has been applied over small areas of the body and on intact skin (Refs. 4 and 6). The potential for sensitization exists, as with any other drug, but is not greater than those of other topical anesthetics, and may possibly be less (Refs. 1 and 5). Primary contact irritancy is low, and rashes and other cutaneous lesions have not been reported. As with other nitrogenous local anesthetics, lidocaine is dispensed as the hydrochloride because of its greater stability and ease of handling.

(2) *Effectiveness.* There are studies documenting the effectiveness of lidocaine hydrochloride as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that lidocaine hydrochloride is effective for use as an OTC external analgesic (Ref. 7).

Lidocaine hydrochloride is very slowly absorbed from the intact skin. The hydrochloride is acidic and is highly ionized; it is not strongly lipophilic and does not readily penetrate the cutaneous epithelial barrier. It is active when it gains access to the deeper cutaneous structures and to the nerve endings, being converted to the base by the buffering mechanisms of tissue fluids in the deeper layers of the skin (Ref. 8).

It stabilizes the axonal membrane and prevents conduction in the nerve fibers connecting with receptors for pain and other stimuli in the skin. Dalili and Adriani (Ref. 6) found that solutions of lidocaine hydrochloride in concentrations up to 4 percent did not obtund the sensation of burning and itch produced by electrical stimulation of the intact skin. However, lidocaine base, which is the physiologically active form, was effective. Additional data on effectiveness is presented in the section on lidocaine (base). (See part III. paragraph B.1.p. above—Lidocaine.)

Lidocaine hydrochloride is effective on damaged skin in concentrations of 0.5 to 4 percent. Claims for effectiveness on intact skin cannot be made for the hydrochloride. Therefore, the Panel does not recommend a dose for use on the intact skin.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 4.0 percent concentration of lidocaine hydrochloride to affected area of broken skin not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 666–669, 1973.

(2) Stecher, P. G., "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 608, 1960.

(3) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(4) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(5) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 277, 1977.

(6) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(7) OTC Volume 060049.

(8) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

r. *Menthol.* The Panel concludes that menthol is safe and effective for use as an OTC external analgesic as specified in the dosage section below. In concentrations of 1.0 percent or less, the ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below. In concentrations exceeding 1.25 percent up to 16 percent, menthol stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Menthol is a secondary alcohol extracted from peppermint oil or made synthetically. Chemically it is hexahydrothymol. Natural menthol is known as peppermint camphor. It may be levorotatory (*l*-menthol) or racemic (*d,l*-menthol). Menthol is slightly soluble in water but soluble in alcohol, ether, chloroform, and mineral oil (Refs. 1 and 2). Menthol may be fatal if ingested in large quantities. Doses of 1 g/kg may be fatal (Ref. 2).

(1) *Safety.* Clinical use has confirmed that menthol is safe in the dosage range used as an OTC external analgesic.

Menthol can cause sensitization in certain individuals. Symptoms include urticaria, erythema, and other cutaneous lesions. However, the sensitization index is low. Menthol has caused asphixia in infants when applied locally for the treatment of coryza (runny nose).

Menthol was used internally as a carminative. Being the active ingredient of peppermint oil, it has found wide acceptance in candy, chewing gum, and cigarettes (Refs. 3 and 4). Menthol has had extensive use in inhalant preparations for the nose and throat. Inhalers containing menthol are commonly used for the relief of nasal congestion, headache, and neuralgia (Ref. 4).

Toxic effects from excessive ingestion of mentholated products can include nausea, abdominal pain, vomiting, and symptoms of central nervous system depression, such as dizziness, staggering gait, flushed face, sleepiness, slow respiration, and coma. The fatal dose of menthol in man is about 2 g (Refs. 5 and 6). Menthol is excreted in the bile and urine as a glucuronide (Ref. 7).

Rakieten et al. studied the effects of menthol vapor on the upper respiratory tract of rats. The rats were exposed to different menthol vapor concentrations over a period of several months. Vapor concentrations of 0.087, 0.148, and 0.295 part per million (ppm) showed no toxic effects, and no significant changes in skeletal muscle, skin, brain, or internal

organs. Animals did show indications of lung irritation when they were exposed to the highest menthol concentrations of 0.259±0.166 ppm (Ref. 8).

When a 20-percent oil solution of menthol is vigorously applied to the skin, an intense and lasting cooling sensation is felt. This is followed by numbness with a slight smarting sensation and hyperemia. Irritation beyond the rubefacient stage does not occur. Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions (Refs. 7 and 9).

In young children, nose drops containing menthol may cause spasm of the glottis. Cases of dangerous asphyxiation have been reported in infants following local application of menthol (Ref. 7). However, clinical experience over many years of use of nose drops containing essential oils, including menthol, have shown no untoward effects (Ref. 10).

Marketing experience with counterirritant products containing menthol attests to the safety of such products. Based upon marketing data supplied by the manufacturers of 7 products, it can be conservatively estimated that more than 32,000,000 dosage units of these products alone were sold in 1972. Customer complaints of 1 per 310,000 were reported by one major manufacturer, while a second reported 1 per 950,000. No complaints of a serious nature were received (Refs. 11 through 17).

It is the opinion of the Panel that although the actual number of adverse effects attributed to the external use of menthol is relatively low, care should be taken to ensure that safety is maintained through adequate packaging, labeling, and application.

(2) *Effectiveness.* There are studies documenting the effectiveness of menthol as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that menthol is effective for use as an OTC external analgesic.

Menthol is used as an antipruritic (Ref. 1) in a concentration range of 0.1 to 1.0 percent. In a higher concentration, it also possesses counterirritant properties; in some cases it merely substitutes one sensation for another. When applied to the skin, menthol stimulates the nerves for perception of cold, while depressing those which perceive pain. Counterirritant concentrations of menthol applied topically produce a preliminary feeling of coolness that is soon followed by a sensation of warmth (Ref. 2). The sensation of cold is not due to cooling of the skin, for the vessels of the treated part are dilated, and a thermometer reading indicates a higher skin temperature than in the other parts of the body (Ref. 18).

The effectiveness of menthol used alone as a counterirritant has been mentioned in many standard texts (Refs. 19 through 22). The irritant (counterirritant) action of menthol varies significantly with the vehicle employed and the method of application. Topical application of a 1-percent solution of menthol in an acetone-alcohol vehicle is often followed by a prompt and persistent feeling of warmth. Other studies have shown that menthol used in combination is also effective (Ref. 17). White and Sage showed that application of a cream containing 15 percent methyl salicylate and 10 percent menthol effectively reduced muscular pain induced by exercise. The counterirritant applied produced skin hyperemia accompanied by the sensation of heat (Ref. 17).

Menthol is usually combined with other ingredients with antipruritic or analgesic properties, such as camphor. Menthol penetrates the intact as well as the damaged skin.

Menthol has been effectively used as a topical analgesic in concentrations ranging from 0.1 to 1.0 percent and as a topical counterirritant in concentrations exceeding 1.25 percent up to 16 percent.

(3) *Dosage*—(i) *For use as a topical analgesic, anesthetic, and antipruritic: For adults and children 2 years of age and older:* Apply a 0.1 to 1.0 percent concentration of menthol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For use as a counterirritant: For adults and children 2 years of age and older:* Apply a concentration of menthol exceeding 1.25 percent up to 16 percent to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* Based upon the dosage, the Panel recommends the applicable Category I labeling for products containing topical analgesic, anesthetic, antipruritic, or counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) "The United States Pharmacopeia," 19th Rev. United States Pharmacopeial Convention, Inc., Rockville, MD., p. 302, 1975.

(2) Osol, A. and R. Pratt, "The Dispensator of the United States," 27th Ed., J. B. Lippinco Co., Philadelphia, pp. 697–698, 1973.

(3) Claus, E., V. Tyler, and L. Brady, "Pharamacognosy," 6th Ed., Lea and Febiger Philadelphia, pp. 211–212, 1970.

(4) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 721, 1975.

(5) Arena, J. M., "Poisoning: Chemistry, Symptoms, Treatments," Charles C. Thomas Publishing Co., Springfield, IL, pp 236–245, 1963.

(6) Deickman, W. B. and H. W. Gerarde, "Symptomatology and Therapy of Toxicological Emergencies," Academic Press New York, p. 251, 1964.

(7) Todd, R. G., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 374, 1972.

(8) Rakieten, N., M. L. Rakieten, and M. Boyd, "Effects of Menthol Vapor on the Intac Animal With Special Reference to the Upper Respiratory Tract," *Journal of the American Pharmaceutical Association, Scientific Edition,* 43:390–392, 1954.

(9) Rudzki, E. and D. Kleniewska, "Kontaktallergie auf einige Lokaltherapeutika und Konservierungsmittel," *Dermatologica,* 143:36–42, 1971.

(10) Adriani, J. and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membrances," *Journal of the American Medical Association,* 162:527–530, 1956.

(11) OTC Volume 060022.

(12) OTC Volume 060023.

(13) OTC Volume 060029.

(14) OTC Volume 060035.

(15) OTC Volume 060050.

(16) OTC Volume 060051.

(17) OTC Volume 060056.

(18) Grollman, A. and E. F. Grollman, "Pharamcology and Therapeutics," 4th Ed., Lea and Febiger, Philadelphia, p. 734, 1960.

(19) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 530, 1971.

(20) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 722, 1975.

(21) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 795, 1955.

(22) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 757, 1976.

s. *Methapyrilene hydrochloride.* The Panel concludes that methapyrilene hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Methapyrilene is an analogue of tripelennamine and of pyrilamine. Chemically, it is *N,N*-dimethyl-*N'*-2-pyridinyl-*N'*-(2-thienylmethyl)-1,2-ethanediamine (Ref. 1). Its structure in many respects resembles that of the nitrogenous topical anesthetics, but there are sufficient modifications from

the classic configuration characteristic of the "caine" type drugs to decrease its potency as a topical anesthetic and to lessen its toxicity systemically (Refs. 2 and 3).

Methapyrilene is a base that forms salts with acids. The two most common salts used clinically are the hydrochloride and the fumarate. The hydrochloride is used topically. It is a white crystalline powder with a faint odor. One g dissolves in 0.5 mL water, 5 ml alcohol, or 3 ml chloroform. It melts at between 161° and 165° C. Pharmacologically, methapyrilene belongs to the class of antihistamine drugs, being similar in its actions and uses to other antihistaminic drugs (Refs. 4 and 5). Methapyrilene hydrochloride was introduced into clinical medicine by Feinberg and Bernstein (Ref. 6).

(1) *Safety.* Clinical use has confirmed that methapyrilene hydrochloride is safe in the dosage range used an an OTC external analgesic.

Methapyrilene hydrochloride is safe and effective as an antipruritic ingredient when applied to damaged skin (Ref. 7). The acute toxicity of methapyrilene hydrochloride is low. The intravenous median lethal dose in mice is 19 mg/kg, and orally, 182 mg/kg. It is somewhat less toxic in mice than tripelennamine but more toxic than diphenhydramine hydrochloride in comparative doses (Ref. 8). The Panel is aware of instances of poisoning following oral ingestion of toxic doses of methapyrilene hydrochloride due to accidental overdosage or deliberate ingestion of massive quantities for suicidal intent. One fatality occurred in a 1-year-old girl who developed hyperpyrexia, cerebral edema, and nephrosis followed by uremia (Ref. 9). When taken orally, methapyrilene causes drowsiness, the most frequent side effect (Ref. 10). Overdosage by any route may produce central nervous system stimulation, followed by depression. Anxiety, hyperative reflexes, and voluntary muscle spasms have been reported following ingestion of toxic doses. Nausea, vomiting, cyanosis, and unconsciousness precede death, following accidental ingestion of an overdose of the drug (Ref. 11). Clinical use and wide marketing experience indicate that even though methapyrilene is absorbed through the skin, side effects do not occur when the ingredient is applied to the skin. The quantity absorbed is not sufficient to cause adverse systemic reactions.

(2) *Effectiveness.* There are studies documenting the effectiveness of methapyrilene hydrochloride as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that methapyrilene hydrochloride is effective for use as an OTC external analgesic.

Methapyrilene hydrochloride, like other antihistaminic drugs, specifically blocks or diminishes the effects of histamine on smooth muscle and on the exocrine glands (Ref. 12). Methapyrilene hydrochloride inhibits the spasmogenic action of histamine on smooth muscle in the bronchioles, gastrointestinal tract, and uterus. Methapyrilene hydrochloride prevents histamine from increasing the permeability of the capillary endothelium, and inhibits the vasodilating action of histamine on the capillaries (Ref. 13). In therapeutic doses, methapyrilene hydrochloride does not inhibit the stimulating action of histamine on gastric secretion. The antiallergic reaction of methapyrilene hydrochloride is due to its antagonistic effect on histamine (Ref. 12). It binds at receptor sites on cells where histamine ordinarily binds, thereby preventing histamine from acting on a cell. Therapeutic doses have no significant effect on blood pressure, heart, and gastrointestinal tract. Methapyrilene hydrochloride protects the body from the effects of exogenous and endogenous histamine (Ref. 13). In comparison to other drugs used in the management of allergic disorders, such as epinephrine or aminophylline, methapyrilene hydrochloride does not overcome the various physiologic responses induced by histamine by an opposing pharmacologic action. Methapyrilene hydrochloride provides symptomatic relief in allergic disorders by protecting the cells from the effects of the free histamine released by pathologic conditions. Any effect that methapyrilene hydrochloride exerts topically is due mostly to its antagonistic effect on histamine. Histamine may be released in the skin and subcutaneous structures due to the action of an antigen-antibody response, and from trauma due to mechanical, chemical, or other causes. It is generally conceded that the receptors occupied by the antihistamine cannot react with free histamine (Ref. 13).

Methapyrilene hydrochloride has a weak anticholinergic and topical anesthetic effect. The anticholinergic effect is of no consequence in considering topical use (Ref. 14). Methapyrilene hydrochloride acts in the same manner as topical anesthetics and does not penetrate the epithelial barrier when the ingredient is applied to the intact skin. Methapyrilene hydrochloride is used orally and topically for symptomatic treatment of pruritus due to urticaria, hay fever, and other allergic disorders caused by histamine release. It is also reported to be useful in some disorders not directly related to histamine release. Sedation is not a problem when the ingredient is used topically on localized areas of the skin, as attested by long marketing experience and clinical usage (Ref. 15). Methapyrilene hydrochloride possesses a feeble topical anesthetic effect. Some of its antipruritic action may be due to its anesthetic action rather than to its antihistaminic effect (Refs. 12 and 13).

Methapyrilene has been used effectively as a topical antipruritic on skin in concentrations of 1 to 2 percent (Ref. 15).

The increasing problem of acquired sensitivity to antihistaminic drugs is presented by Ellis and Bundick (Ref. 16). These authors indicate that the antipruritic action of topical antihistaminic drugs is most useful for 1 to 2 weeks to prevent continued trauma or scratching, and thereby permit permanent healing. However, these drugs frequently lose efficacy after 3 or 4 weeks. Methapyrilene hydrochloride is no exception. Sensitivity often develops after this period of use. The Panel does not recommend use of methapyrilene hydrochloride for longer than 7 days except under the advice and supervision of a physician.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 to 1 percent concentration of methapyrilene hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 777, 1976.

(2) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(3) Adriani, J. and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membrances," *Journal of the American Medical Association,* 162:527–530, 1956.

(4) "AMA Drug Evaluations—1971," 1st Ed., American Medical Association, Chicago, p. 103, 1971.

(5) "AMA Drug Evaluations—1971," 1st Ed., American Medical Association, Chicago, pp. 657–674, 1971.

(6) Feinberg, S. and T. Bernstein, "Histamine Antagonists," *Journal of*

Laboratory and Clinical Medicine, 32:1370–1373, 1947.

(7) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 559, 1957.

(8) Lee, H. M., W. G. Dinwiddie, and K. K. Chen, "The Antihistamine Action of N-(2-Pyridyl)-N-(2-Thenyl)-N',N'-Dimethylethylenediamine Hydrochloride," *Journal of Pharmacology and Experimental Therapeutics,* 90:83–87, 1947.

(9) Wyngaarden, J. B. and M. H. Seevers, "The Toxic Effects of Antihistamine Drugs," *Journal of the American Medical Association,* 145:277–282, 1951.

(10) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 673–675, 1977.

(11) Fattek, A. and J. B. Dudley, "Fatal Poisoning Involving Methapyrilene," *Journal of the American Medical Association,* 219:756–757, 1972.

(12) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 608, 1975.

(13) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 147, 723, 1973.

(14) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology,* 17:223–242, 1977.

(15) OTC Volume 060141.

(16) Ellis, F. A. and W. R. Bundick, "Appraisal of Topical Use of Antihistamines," *Journal of the American Medical Association,* 150:773–776, 1950.

t. *Methyl nicotinate.* The Panel concludes that methyl nicotinate is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Methyl nicotinate is the methyl ester of nicotinic acid prepared synthetically by passing hydrochloric acid gas into a hot methanol solution of nicotinic acid. The drug occurs as colorless crystals with a melting point of 39° C and is soluble in water, alcohol, and benzene (Ref. 1).

(1) *Safety.* Clinical use has confirmed that methyl nicotinate is safe in the dosage range used as an OTC external analgesic.

Nicotinic esters administered parenterally or rectally to test animals provided evidence of very low toxicity (Ref. 2). The oral LD_{50} for mice was 310 mg/kg (Ref. 3).

When applied over large skin surfaces of a susceptible person, various concentrations of nicotinate counterirritants may produce generalized vascular dilatation as evidenced by a fall in blood pressure, change in pulse rate, and syncopy (Ref. 3).

Marketing data reveals that 3 manufacturers of counterirritant products containing methyl nicotinate sold more then 2,700,000 units in 1972. In all, they received 16 customer complaints, all of them minor (Refs. 2, 3, and 4).

(2) *Effectiveness.* There are studies documenting the effectiveness of methyl nicotinate as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that methyl nicotinate is effective for use as an OTC external analgesic.

Although nicotinic acid is inactive in topical applications, its esters possess a marked power of diffusion and readily penetrate the cutaneous barrier (Ref. 5). Vasodilation results from very low concentrations. The rate of absorption differed among various vehicles, but duration of reaction showed an inverse relationship to the rate of absorption (Ref. 6). The rate of absorption is accelerated by increased ambient temperatures. Alteration of concentrations between 0.25 and 1.0 percent does not change the rate of absorption, but does increase the intensity of the reaction.

Fulton and associates studied the mechanism of action of methyl nicotinate and other rubefacients. They used the cheek pouch of the hamster and observed for response of microcirculation. Vasodilation was produced consistently by ethyl, methyl, *n*-hexyl, and tetrahydrofurfuryl esters of nicotinic acid applied topically to the walls of arterioles in concentrations ranging from 1 to 100 percent (Ref. 7).

Application to human subjects produced erthema with skin temperature elevation corresponding to the degree of erythema produced (Ref. 8).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.25 to 1.0 percent concentration of methyl nicotinate to the affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 795, 1975.

(2) OTC Volume 060029.

(3) OTC Volume 060077.

(4) OTC Volume 060033.

(5) Stoughton, R. B., W. E. Clendenning, and D. Kruse, "Percutaneous Absorption of Nicotinic Acid and Derivatives," *Journal of Investigative Dermatology,* 35:337–340, 1960.

(6) Fountain, R. B., B. S. Baker, J. W. Hadgraft, and I. S. Sarkany, "The Rate of Absorption and Duration of Action of Four Different Solutions of Methyl Nicotinate, "*British Journal of Dermatology,* 81:202–206, March, 1969.

(7) Fulton, G. P., E. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *Journal of Investigative Dermatology,* 33:317–325, 1959.

(8) Peterson, J. B., E. M. Farber, and G. P. Fulton, "Responses of the Skin to Rubefacients," *Journal of Investigative Dermatology,* 35:57–64, 1960.

u. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe and effective for use as an OTC external analgesic as specified in the dosage section discussed below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below. There are no data to confirm any claims that methyl salicylate depresses cutaneous sensory receptors in the same way as the topical analgesics. Therefore the Panel has not considered methyl salicylate as a topic analgesic.

Methyl salicylate is the methyl ester of salicylic acid. Before the discovery of methods for synthesizing methyl salicylate, it was produced by steam distillation from natural sources. The natural source products are known as gaultheria oil, betula oil, sweet birch oil, teaberry oil, and wintergreen oil. These products when pure are as effective as the synthetic product. Today, these names are considered synonymous with methyl salicylate, which is prepared synthetically by esterification of salicylic acid with methanol.

Methyl salicylate is a volatile liquid having a density of 1.18 g/mL. One mL of methyl salicylate has a salicylate content equivalent to 1.4 g aspirin. It is a colorless, yellowish, or reddish, oily liquid and is miscible with alcohol, ether, and chloroform. It is only slightly soluble in water and not highly volatile (Ref. 1).

Methyl salicylate boils at between 220° to 224° C. At low concentrations, methyl salicylate is used as an organoleptic agent for both its condimental flavor and pleasing aroma. Methyl salicylate acts as a counterirritant for the temporary relief of deep-seated pain (Refs. 2 through 6). Methyl salicylate penetrates intact skin after topical application. Some available data suggest that the amounts absorbed percutaneously act systemically and are sufficient to have significant analgesic activity (Refs. 7 through 10).

(1) *Safety.* Clinical use has confirmed that methyl salicylate is safe in the

dosage range used as an OTC external analgesic.

The Panel has given much consideration to the toxicity of methyl salicylate. The American Medical Association has linked methyl salicylate's candy-like odor (wintergreen, teaberry flavors) to children's ingestion of toxic quantities of drug products containing therapeutic amounts of methyl salicylate (Ref. 11). But a review of the data on poisoning from the National Clearinghouse of Poison Control Centers (Bethesda, Maryland) for the period of 1970 to 1972 concerning oral ingestion of methyl salicylate primarily in ointment formulations indicates that there were no deaths and a lack of cases manifesting severe symptoms. Recent regulations require the use of child-resistant containers for liquid preparations containing more than 5 percent methyl salicylate (16 CFR 1700.14(a)(3)). These containers cause some inconvenience for arthritic and rheumatic patients, but they provide an important safeguard for small children, who are the most common victims of accidental poisoning caused by toxic household medicinal substances.

Except for the fact that it can cause severe local irritations, ingested methyl salicylate is not notably different in its toxic actions from other salicylates. Metabolic acidosis may be a more prominent complication with the methyl ester than with other derivatives of salicylic acid (Ref. 12). The average lethal dose of methyl salicylate is estimated to be 10 mL for children and 30 mL for adults (Refs. 13 and 14). But the ingestion of as little as 4 mL (4.7 g) methyl salicylate has caused death in children (Ref. 15). For comparative purposes, it should be noted that 4 mL (4.7 g) methyl salicylate is equivalent in salicylate content to 4.3 g salicylic acid, 4.96 g sodium salicylate, or 5.6 aspirin, and that death has ensued following the ingestion of 3 g salicylic acid and 4 g sodium salicylate (Ref. 16). The toxic dose of aspirin is estimated to range from 75 to 150 mg/kg. This is in the range of 5.3 to 10.5 g for a 154–1b adult.

The Panel has carefully considered the benefit-to-risk potential of topically adminstered methyl salicylate in arriving at its conclusion concerning safety and effectiveness, and has recommended appropriate precautionary labeling elsewhere in this document. (See part III. paragraph B.1. below—Category I Labeling.) There is adequate evidence that ingestion of more than small condimental amounts of methyl salicylate is hazardous, but little to suggest that these toxicity hazards restrict the rational topical use of the drug as a counterirritant.

Methyl salicylate has a high degree of safety for topical use. The manufacturers of 10 counterirritant OTC drug products provided marketing data on thier sales through 1972. Their data show that in 1972 they marketed more than 35,000,000 individual packages containing methyl salicylate. No customer complaints of a serious nature were received by these manufacturers. Minor complaints were about 1 out of 500,000 (Refs. 17 through 26).

(2) *Effectiveness.* There are studies documenting the effectiveness of methyl salicylate as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that methyl salicylate is effective for use as an OTC external analgesic.

Using a single-blind technique, Brusch (Ref. 27) compared a topical lotion containing methyl salicylate with placebo lotion on a test group of 203 arthritic patients. Both the placebo and the test lotion producted improved comfort levels. However, significantly greater improvement resulted from the use of the counterirritant lotion.

In a double-blind study, the effect of a counter-irritant lotion containing methyl salicylate was compared with a placebo in 62 individuals suffering from moderately painful arthritis. The methyl salicylate-containing lotion was significantly superior to the placebo in reducing the arthritic pain (Ref. 27).

Chronic muscle pain is a component of arthritic pain. Sustained hypertonicity of skeletal muscles results in chronic muscle pain. The resting muscle action potential can be determined by use of the electromyograph and can be used to measure the degree of muscle tone. Application of a topical ointment containing methyl salicylate to painful arthritic joints of a test group of 30 individuals produced a significant decrease in the muscle action potential in the adjacent muscles, whereas the application of a placebo produced no significant change (Ref. 28).

Counterirritant methyl salicylate products are used extensively in the management of muscle pain. A test group of 40 healthy individuals performed fatiguing exercise which produced muscle soreness in both forearms. Forty-eight hours later, the muscle action potential was determined on each individual's forearm, followed by the application of a placebo to one forearm and the application of a counterirritant ointment containing methyl salicylate to the other. Postmedication muscle action potentials showed a significant decrease of hypertonicity in the treated forearms and little change in the placebo-treated control forearms (Ref. 29).

Methyl salicylate is one of the most widely used single ingredients considered by the Panel. It is not only a component of a large number of OTC products for self-medication, but is also the most widely used ingredient in "locker-room" atheletic rubs.

In addition to the numerous proprietary products containing methyl salicytate, a considerable number of nonproprietary formulas may be found published in the older official compendia of the United States and Great Britain. The Extra Pharmacopoeia (Ref. 30) lists nine such formulas, four ointments and five liniments. The methyl salicylate content in these ointments ranges from 12.5 to 50.0 percent by weight, and from 25 to approximately 65 percent by volume in the five liniments. A concentration of 100 percent, undiluted methyl salicylate had been used for many years as a counterirritant for relieving pain of sore muscles and sprains, and for the symptomatic treatment of painful rheumatoid arthritis, rheumatic fever, and the like (Ref. 31). In considering the benefit-to-risk ration, however, the Panel believes that using concentrations of methyl salicylate exceeding 60 percent by weight (50 percent by volume) increases the hazards without significantly increasing the therapeutic benefits. Therefore, the 60-percent maximum concentration is chosen by the Panel in the interest of safety. Concentrations of less than 10 percent are not effective irritants.

Methyl salicylate has been effectively used in concentrations ranging from 10 to 60 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 10 to 60 percent concentration of methyl salicylate to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 743–744, 1957.

(2) Krantz, J. C., Jr. and C. J. Carr, "Pharmacological Principles of Medical Practice," 6th Ed., The Williams and Wilkins Co., Baltimore, p. 200, 1965.

(3) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 993, 1970.

(4) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 562–563, 1970.

(5) Fulton, G. P., E. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *The Journal of Investigative Dermatology,* 33:317–325, 1959.

(6) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 1036, 1971.

(7) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 749–750, 1973.

(8) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 987–1001, 1970.

(9) Crossland, J., "Lewis's Pharmacology," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 560, 1970.

(10) Beutner, R., B. Calesnick, E. Powell, and L. Bortin, "On the Absorption and Excretion of Methylsalicylate Administered by Inunction," *Journal of Laboratory and Clinical Medicine,* 28:1655–1663, 1943.

(11) Anon., "Candy Medication and Accidental Poisoning," *Journal of the American Medical Association,* 158:44–45, 1955.

(12) Davison, C., E. F. Zimmerman, and P. K. Smith, "On the Metabolism and Toxicity of Methyl Salicylate," *Journal of Pharmacology and Experimental Therapeutics,* 132:207–211, 1961.

(13) Deichman, W. B. and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 662, 1969.

(14) Wilson, C. O., O. Gisvold, and R. F. Doerge, "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 5th Ed., J. B. Lippincott Co., Philadelphia, p. 675, 1966.

(15) "The Year Book of Drug Therapy—1969," Edited by Beckman, H., Year Book Medical Publishers, Chicago, p. 268, 1969.

(16) Thienes, C. H. and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 80, 1972.

(17) OTC Volume 060022.

(18) OTC Volume 060023.

(19) OTC Volume 060029.

(20) OTC Volume 060030.

(21) OTC Volume 060031.

(22) OTC Volume 060040.

(23) OTC Volume 060050.

(24) OTC Volume 060051.

(25) OTC Volume 060056.

(26) OTC Volume 060077.

(27) OTC Volume 060036.

(28) White, J. R. and J. M. Sage, "Effects of a Counterirritant on Muscular Distress in Patients with Arthritis," *Physical Therapy,* 51:36–42, 1971.

(29) White, J. R. and J. M. Sage, "Topical Analgesic on Induced Muscular Pain," *Physical Therapy,* 50:166–172, 1970.

(30) Todd, R. G., "Martindale, The Extra Pharmacopeia," 25th Ed., The Pharmaceutical Press, London, pp. 1262–1263, 1972.

(31) Lyght, C. E., "The Merck Manual of Diagnosis and Therapy," 11th Ed., Merck and Co., Rahway, NJ, p. 1545, 1966.

v. *Phenol.* The Panel concludes that phenol is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Phenol is hydroxybenzene. Phenol was discovered in 1834 in coal tar by Ringe who named it "carbolic acid." It was also once called phenic acid (Ref. 1). Phenol is a primary alcohol of the aromatic series and as such exerts a topical anesthetic action (Ref. 2). Although it may be obtained from coal tar, most of it is now prepared synthetically. The antimicrobial efficacy of phenol was first demonstrated by Lister in 1857. Now it has limited clinical use. It is used most often as a topical analgesic and for cauterization (Ref. 3). Compounds less toxic than phenol are more effective antimicrobial agents (Ref. 1). Phenol consists of colorless to light-pink, needle-shaped crystals interlaced or separated, or as a white to light-pink crystalline mass (Ref. 4). It possesses a distinctive aromatic odor. It gradually darkens on exposure to light and air. Phenol is liquefied by warming or by the addition of 10 percent water. It is caustic if applied directly to tissues (Ref. 1). A concentrated solution of phenol and water has a strength of approximately 6 percent. Phenol is soluble in alcohol, glycerin, chloroform, ether, and fixed and volatile oils (Ref. 4). It is sparingly soluble in mineral oil. One g dissolves in about 5 mL of water. Solutions of phenol are oxidized and turn brown due to the formation of quinones (Ref. 1). With sodium hydroxide, phenol forms a salt that is ionized and highly alkaline. Phenol boils at about 182° C. It congeals at temperatures lower than 39° C. Phenol combines with camphor to form a substance known as camphor-phenol (Ref. 5). Whether this is a definite chemical complex or a solution of phenol in camphor has not been established. The mixture releases phenol slowly in small quantities. The presence of moisture hastens the process (Ref. 1).

(1) *Safety.* Clinical use has confirme that phenol is safe in the dosage range used as an OTC external analgesic.

Concentrations greater than 2 perce in aqueous solutions are irritating and may cause sloughing and necrosis (Re 3 and 6). When applied in pure form to the skin, phenol causes an area of blanching. A feeling of numbness develops. Later the area undergoes necrosis and sloughing (Ref. 1).

After oral ingestion or absorption, phenol is oxidized and conjugated wit sulfuric, glucuronic and other acids by the liver and excreted into the urine. Only small quantities of free phenol ar excreted into the urine. Phenol is lipophilic and is readily absorbed through the intact and damaged skin and passes into the systemic circulatio (Ref. 7). Absorption through the skin depends upon the area exposed rather than on the concentration (Refs. 3 and 8). Concentrated solutions are toxic an cause death if ingested orally (Ref. 8). Phenol has been used for suicidal purposes. Cases of accidental poisonin have been common. The symptons of toxicity usually develop rapidly and death has occurred within 2 or 3 minut after ingestion. Coma and collapse are the main signs of toxicity from large doses. After ingestion of small amount the most common symptoms are nause vomiting, collapse, pallor, cold sweats, and feeble pulse. Stupor ensues, deepening into a comatose state with insensibility. Respirations are often rapid and shallow, irregular, and sometimes paroxysmal. Death results from respiratory arrest. Paralysis of bo sensation and motion may occur. In some cases, violent clonic or epileptiform convulsions have occurred The urine is generally scanty, albuminous, and greenish or black in color. The diagnosis is usually not difficult to make, since the odor of phenol can be detected on the breath and in the smoky urine. White, corrugated spots are present on the mucous membranes of the mouth and throat due to the caustic action of the phenol. The estimated fatal dose of phenol is approximately 15 g. However, death has been reported following the ingestion of as little as 1.5 g. Recovery has followed the ingestion of as much a 30 g. Death usually occurs from respiratory failure, although in some instances fatal cardiac failure has been reported. The degree of toxicity depend upon the amount of phenol ingested; its concentration is not an important consideration (Refs. 1 and 8).

Some question exists concerning the carcinogenic potential of phenol (Ref. 9) How important this finding may be in

regard to the use of phenol on the human skin is unknown.

This issue was addressed in the tentative final order on OTC Topical Antimicrobial Products, published in the **Federal Register** of January 6, 1978 (43 FR 1210), as follows:

"The Commissioner recognizes that the accepted protocol for determining the potential for the carcinogenicity or cocarcinogenicity (tumor promotion) of any drug is the National Cancer Institute (NCI) standard bioassay program. Phenol has been included in this program, but the results are not yet available. The Commissioner will carefully review the results of the NCI study and will determine at that time whether any regulatory action is appropriate.

Chronic ingestion of phenol in small quantities may produce a dark discoloration of the tissues, particularly cartilage.

(2) *Effectiveness.* There are studies documenting the effectiveness of phenol as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that phenol is effective for use as an OTC external analgesic.

Phenol penetrates the sensory nerve endings and exerts its analgesic and anesthetic effect in a manner that is not clearly understood (Refs. 6 and 7). It is a polar substance and is thought to act in the same manner as the "caine" type of topical anesthetics (Ref. 10). The hydrocarbon pole is lipophilic and orients into the lipid phase of the axon. The hydroxyl group is hydrophilic and orients into the water phase (Ref. 11). Phenol is acidic and forms salts with alkalies. When combined with the nitrogenous basic topical anesthetics, it may nullify their effects by lowering the pH (Ref. 12). Its absorption from the skin does not depend upon the pH of the medium. A feeling of warmth and tingling ensues following the application of 5 percent phenol to the unabraded skin. Complete topical anesthesia eventuall develops and the area becomes irritated. In many cases, phenol can be very irritating, even caustic, to the skin and can cause necrosis in concentrations of more than 2 percent in water. It possesses topical anesthetic activity and acts as an antipruritic when aded to dermatologic preparations in concentrations of 0.5 to 2.0 percent (Refs. 2 and 10). The blockade produced in concentrations of less than 2 percent is reversible. Aqueous solutions stronger than 2 percent are too irritating for topical application to the skin. A 4-percent solution in glycerin is sometimes used and is said not to have caustic properties. When camphor is added to phenol, a liquid forms. This reduces the severity of the topical reaction and the absorption of phenol, apparently due to its camphor-holding property (Ref. 5). Phenol is employed topically as a keratolytic, neurolytic, and a destructive agent in concentrations of 10 percent to 40 percent (Ref. 1).

Phenol is analgesic and anesthetic to the mucous membranes. A 5-percent solution of phenol and water has definite topical anesthetic action, but sloughing occurs in about 10 percent of the cases (Ref. 13).

A 5-percent solution of phenol in 95 percent alcohol is an efficient topical anesthetic. Complete anesthesia results in 53 percent and partial anesthesia in 47 percent. However, slough or superficial necrosis resulted in 22 percent of cases studied.

Dressings or compresses saturated with solutions of phenol, even though dilute, may cause sloughing, and are not recommended. Preparations containing 1 to 2 percent phenol should be applied only to the smallest area needing treatment and should not be bandaged to prevent severe skin irritation.

When phenol is combined with other topical anesthetics of the nitrogenous type that are active in the basic form on the skin, conversion of the nitrogenous base form of the anesthetic to the acid form by the phenol may nullify their action and not necessarily produce an additive effect or summation. The antimicrobial activity of phenol is due to its ability to coagulate proteins.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 2.0 percent concentration of phenol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not apply this product to extensive areas of the body or under compresses or bandages."

References

(1) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1037–1038, 1955.

(2) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology,* 17:223–242, 1977.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 892–893, 1977.

(4) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 940, 1976.

(5) OTC Volume 060053.

(6) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 900–901, 1973.

(7) Freeman, M. V., J. H. Draize, and E. Alvarez, "Cutaneous Absorption of Phenol," *Journal of Laboratory and Clinical Medicine,* 38:262–266, 1951.

(8) Deichman, W. B., "Local and Systemic Effects Following Skin Contact with Phenol-A Review of the Literature," *Journal of Industrial Hygiene and Toxicology,* 31:146–154, 1949.

(9) Boutwell, R. K. and D. K. Bosch, "The Tumor-Producing Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research,* 19:413–424, 1959.

(10) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(11) Adriani, J., "Local Anesthetics," *in* "The Pharmacology of Anesthetic Drugs," 5th Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 131–145, 1970.

(12) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

(13) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, pp. 990–991, 1975.

w. *Phenolate sodium.* The Panel concludes that phenolate sodium is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Phenolate sodium, also known as sodium phenoxide, sodium phenate, sodium carbolate, and phenol sodium, is the sodium salt of phenol (carbolic acid) (Ref. 1). Ordinarily, phenol exists in the enol form, that is, a benzene ring with a hydroxyl group. Phenol has high resonant energy and can revert to the keto form (Ref. 2). The keto form is less stable than the enol form. The sodium salt is formed with the keto form. One hydrogen atom on position 2 is replaced by the metallic ion. Phenols are more acidic than other alcohols or water but are weaker acids than carboxylic and carbonic acids. The dissociation constant of phenol is 1.3×10^{10} compared to 4.3×10^{7} for carbonic acid. Phenol reacts with sodium hydroxide to form a water-soluble salt, but it will not interact with sodium carbonate to form the salt.

Phenolate sodium is a white to reddish deliquescent substance composed of rods or granules. If exposed to air, it is readily decomposed by carbon dioxide to phenol and sodium carbonate. It must be stored in tightly

closed containers Phenolate sodium is strongly alkaline and caustic. It is soluble in water and alcohol. Aqueous solutions are strongly alkaline and caustic. Phenolate sodium releases 81 percent phenol on decomposition or acidification. The therapeutic and toxic effects of phenolate sodium are due to the phenol released (Refs. 1, 2, and 3).

(1) *Safety.* Clinical use has confirmed that phenolate sodium is safe in the dosage range used as an OTC external analgesic.

The safety considerations for phenolate sodium are the same as those for phenol because phenolate sodium releases phenol, and its toxic effects are due to the phenol (Ref. 1). Phenolate sodium may augment the caustic effects of phenol if concentrated solutions are ingested orally or applied topically. This is due to the presence of sodium hydroxide, from which phenolate sodium is formed. Phenolate sodium precipitates proteins and can, therefore, exert an antimicrobial effect as does phenol. The Panel has not considered the antimicrobial effects of phenol or phenolate sodium. Phenolate sodium, in doses of 0.1 to 0.3 g, was formerly used to treat diarrhea.

(2) *Effectiveness.* There are studies documenting the effectiveness of phenolate sodium as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that phenolate sodium is effective for use as an OTC external analgesic.

Aqueous solutions of phenolate sodium are alkaline and caustic, but dilute solutions can be used to obtain the same analgesic, anesthetic, and antipruritic effect as phenol (Ref. 1). Because solutions containing phenolate sodium are alkaline, the effects of certain ingredients that are active physiologically in the form of a base, as is the case with nitrogenous topical anesthetics, is assured. The released phenol and alkali may enhance the effects of the latter compounds and maintain an alkaline medium. Aqueous solutions of phenolate sodium have been used as a topical analgesic applied in the form of bandages. It has also been used combined with linseed oil in a ratio of 1:5 phenolate sodium-linseed oil. Phenolate sodium is not used as the sole ingredient in any of the products submitted to the Panel for consideration but has been submitted in combination with other external analgesic ingredients.

Phenolate sodium has been used effectively as an external analgesic on the skin in concentrations of 0.25 to 2.0 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 2.0 percent concentration of phenolate sodium to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Stecher, P. G., "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 958, 1960.

(2) Noller, C. R., "Chemistry of Organic Compounds," W. B. Saunders Co., Philadelphia, pp. 489–490, 1951.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1118, 1976.

x. *Pramoxine hydrochloride.* The Panel concludes that pramoxine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Pramoxine, also known as pramocaine and proxazocain, is a tertiary amine that combines with acids to form salts. It interacts with hydrochloric acid to form the hydrochloride, which is the form used in OTC products (Ref. 2). The drug first became available in 1952.

Pramoxine is 4[3-(*p*-butoxyphenoxy)]-propyl morpholine and differs from the usual type of nitrogen-containing topical anesthetics because its chemical structure departs from that of the "caine" type drugs. Unlike them, it is neither an ester nor an amide. Pramoxine base is a liquid that boils at 183° to 184° C (Ref. 1). Pramoxine hydrochloride is a white crystalline powder that melts at 181° to 183° C. It is freely soluble in water and alcohol, and is insoluble in ether. Data on the lipophilic nature of the base are not available.

(1) *Safety.* Clinical use has confirmed that pramoxine hydrochloride is safe in the dosage range used as an OTC external analgesic.

The systemic toxicity of pramoxine hydrochloride is of a low order (Ref. 2). The intravenous LD_{50} in rats is 79.5 mg/kg. The compound appears to be relatively nontoxic when studied in laboratory animals. The intravenous administration of 5 mg/kg to anesthetized rats, cats, dogs, and monkeys produced only transient mild depression of the blood pressure. Othe studies using rats, mice, and guinea pi involving both intraperitoneal and subcutaneous routes reveal few toxic effects unless extremely large doses ar used (up to 942 mg/kg) (Ref. 3). The orally ingested lethal dose for man is n known. Only one report of alleged toxicity was received by the manufacturer from August 1954 to January 1973. A child ingested approximately 10 grams of the product orally without any adverse effects or sequellae (Ref. 3). Pramoxine hydrochloride, despite its low order of toxicity, is not suitable for injection an can irritate tissues and delicate mucou membranes. It should not be used in th eye, nose, or for bronchoscopy or gastroscopy. Systemic absorption does not cause the characteristic reactions, such as convulsions, cardiac depressio etc., ascribed to the "caine" type drugs. Although pramoxine hydrochloride has a local irritating effect on certain mucous membranes and produces burning if applied to the eye, it is not irritating to the skin. Sensitization may occur, but it is no more common than with other topical anesthetics in other chemical groups. Chronic toxicity studies reveal no alteration in the heart liver, or kidney (Ref. 3).

(2) *Effectiveness.* There are studies documenting the effectiveness of pramoxine hydrochloride as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that pramoxine hydrochloride is effective for use as an OTC external analgesic.

Like other topical anesthetics, pramoxine hydrochloride acts by stabilizing the neuronal membrane of the nerve ending with which it comes into contact, thus blocking painful sensations due to burns, cuts, and abrasions (Ref. 4). Its onset of action on mucous membranes requires several minutes. It is ionized and does not penetrate the intact skin unless it is converted to the base (Ref. 5). It causes analgesia on the skin (Ref. 3) but the sensation of numbness is not obtained unless deeper layers of the skin are exposed. Pramoxine hydrochloride obtunds the sensation of itch and is an effective antipruritic agent on damaged skin. Dalili and Adriani (Ref. 5) found that 1 percent ointment, when applied t intact skin and skin that had been burned with ultraviolet light, did not obtund the sensation of burning and itching elicited by electrical stimulation.

Pramoxine hydrochloride has been effectively used on damaged skin in concentrations ranging from 0.5 to 1.0 percent (Ref. 3).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 1.0 percent concentration of pramoxine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co, Rahway, NJ, p. 997, 1976.

(2) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 951, 1973.

(3) OTC Volume 060045.

(4) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 390–391, 1976.

(5) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

y. *Resorcinol.* The Panel concludes that resorcinol is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Resorcinol, also known as resorcin, is metadihydroxybenzene, an aromatic alcohol, and, therefore, it is a phenolic type compound (Ref. 1). Resorcinol was first prepared by Hlasiwetz and Barth in 1864. It may be prepared by fusing benzene disulfonic acid with sodium hydroxide. Resorcinol is chemically allied to pyrocatechol, which is the *ortho*-dihydroxybenzene, and hydroquinone, which is *para*-dihydroxybenzene. Resorcinol occurs as white, or nearly white, needle-shaped crystals or as a powder. It has a faint, characteristic aromatic odor. When initially applied to the tip of the tongue, it imparts a sweetish taste that is promptly followed by a bitter taste. Resorcinol melts at between 109° and 111° C. A 1:20 concentration of an aqueous solution is acidic. One g of resorcinol dissolves in 1 mL of water and approximately 1 mL of alcohol. It is freely soluble in glycerin and ether but only slightly soluble in chloroform. Resorcinol powder acquires a pink tint on exposure to light and air. An aqueous solution of resorcinol first turns pink, then red, and finally brown on exposure to light and air, due to oxidation to quinones. The change is hastened by alkalies. Oxidizing agents produce a red or violet color. A liquid or soft mass results from the trituration with camphor, menthol, phenol, chloral hydrate, acetanilid, antipyrine, and other substances. Resorcinol has been obtained from sagapenum, asafetida, ammoniac, etc. The present-day compound is prepared synthetically as described above (Ref. 2).

Resorcinol can be acetylated to form the acetyl monoacetate. The action of resorcinol monoacetate is similar to that of resorcinol because of the gradual liberation of the latter due to a slow hydrolytic reaction that occurs. The effects, therefore, are milder and longer lasting than those of the unacetylated derivative (Ref. 1).

(1) *Safety.* Clinical use has confirmed that resorcinol is safe in the dosage range used as an OTC external analgesic.

Resorcinol resembles phenol in its physiologic properties. However, it is less toxic than phenol (Refs. 3 and 4). Topically, resorcinol is a protein precipitant (Ref. 5). Because of this action, it possesses an antimicrobial action. Resorcinol will darken white, blonde, or gray hair (Ref. 1). After oral ingestion, resorcinol causes depression of the central nervous system and an elevation in blood pressure.

In concentrations of 1 to 6 percent, resorcinol is not a primary irritant. But concentations exceeding 10 percent may cause severe skin irritation (Ref. 6). Resorcinol is readily absorbed from the intact and damaged skin. As is the case with phenol, absorption of resorcinol does not depend upon the pH of the medium in which it is incorporated. In concentrations above 6 percent, it causes skin irritation manifested by hyperemia, itching, edema, corrosion, and loss of superficial layers of the skin (Ref. 2). Topical exposure to high concentrations causes systemic absorption resulting in enlargement of regional lymph nodes.

Poisoning can occur from the ingestion of resorcinol. Manifestations are restlessness, cyanosis, convulsions, tachycardia, and dyspnea. Death is caused by respiratory failure. If resorcinol is absorbed in large quantities when it is applied topically, it causes methemoglobinemia (Ref. 2).

The minimum lethal dose of resorcinol is 400 to 500 mg/kg subcutaneously in guinea pigs, 340 to 360 mg/kg in mice subcutaneously, and 400 to 500 mg/kg in rats subcutaneously. In dogs, the median lethal dose intravenously is 700 to 1,000 mg/kg. The oral median lethal dose in rabbits is 750 mg/kg, and in rats and guinea pigs it is 370 mg/kg (Ref. 2).

Although resorcinol is much less toxic than phenol, cases of poisoning have been reported, with some fatalities. Cunningham (Ref. 7) reviewed the literature and found eight cases of poisoning, mostly in children. Six of the eight cases were fatal. In addition, he reviewed a case in which a 7-week-old child developed severe hemolytic anemia. He concluded that the use of resorcinol, even in low concentrations in weak lotions or ointments, on the skin of babies and young children was dangerous. Absorption may be intense and lethal quantities absorbed if applied to extensive areas of the damaged skin. Bull and Fraser (Ref. 8) reported three cases of myxedema associated with varicose ulcers to which resorcinol ointment had been applied. They concluded that when resorcinol was absorbed through the ulcer it acted as an antithyroid agent. Pascher (Ref. 9) cities two cases of resorcinol toxicity in young adults with pustular acne. A 40-percent concentation was applied from 1 to 4 hours over 33 and 22 days, respectively. The urine was violet-black. Both patients recovered.

Resorcinol has keratolytic properties and causes exfoliation of the skin (Ref. 2).

Resorcinol can act as a paptene and produce sensitization, although the Panel finds that the incidence of allergic reactions following its use is low (Refs. 10, 11, and 12). One product submitted for review has been on the market for 78 years without any report of substantial toxicity (Ref. 10).

(2) *Effectiveness.* There are studies documenting the effectiveness of resorcinol as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that resorcinol is effective for use as an OTC external analgesic.

Because resorcinol is an aromatic alcohol and resembles phenol in many of its qualities, it would be expected to demonstrate the antipruritic effects that phenol does (Ref. 1).

Resorcinol has bactericidal and fungicidal activity. Because resorcinol is a phenol, it belongs to the hydroxy group of topical anesthetics and acts in the same manner as other hydroxy compounds (Refs. 1, and 3 through 5). Resorcinol produces no significant degree of anesthesia when applied in concentrations of less than 6 percent to

the intact skin but is effective as an antipruritic (Refs. 1, and 3 through 5).

Resorcinol was formerly used as an intestinal antiseptic in enteritis, but it is doubtful that it was effective in these situations. It has been used in concentrations ranging from 2 to 5 percent as a gastric lavage or as a wash in nasal cararrh, otitis externa, chronic colitis, leukoplakia, and other inflammations of the mucous membranes (Ref. 2). The Panel merely mentions these uses and does not condone the use of resorcinol for these purposes.

Resorcinol is an antipruritic in solutions of 0.5 to 3.0 percent (Ref. 3).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 3.0 percent concentration of resorcinol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not apply this product to large areas of the body."

References

(1) Osol, A., "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1017–1018, 1973.

(2) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1184–1185, 1955.

(3) Grollman, A., "Pharmacology and Therapeutics," 6th Ed., Lea and Febiger, Philadelphia, p. 816, 1965.

(4) Krantz, J. C. and C. J. Carr, "The Pharmacologic Principles of Medical Practice," 7th Ed., The Williams and Wilkins Co., Baltimore, p. 775, 1969.

(5) Goodman, L. S. and A. Gilman, "The Pharmacologic Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, p. 991, 1975.

(6) Boyd, E. M., "Dermatomucosal Agents," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill Book Co., New York, p. 1036, 1971.

(7) Cunningham, A. A., "Resorcin Poisoning," *Archives of Disease in Childhood,* 31:173–176, 1956.

(8) Bull, G. M. and R. Fraser, "Myxedema from Resorcinol Ointment Applied to Leg Ulcers," *Lancet,* 258(1):851–855, 1950.

(9) Pascher, F., "Systemic Reactions to Topically Applied Drugs," *Bulletin of the New York Academy of Medicine,* 49:613–617, 1973.

(10) OTC Volume 060038.

(11) OTC Volume 060060.

(12) OTC Volume 060123.

z. *Tetracaine.* The Panel concludes that tetracaine is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Tetracaine is one of the numerous soluble aminobenzoic acid esters possessing local anesthetic activity. Tetracaine is closely allied to procaine in chemical structure (Ref. 1). It has also been known as amethocaine, pantocaine, decicaine, certacaine, and anethcaine (Ref. 2). It has been available since 1932 for spinal nerve blocks, epidural nerve blocks, and topical anesthesia. In the structure of tetracaine, a butyl group is substituted for one of the hydrogen atoms of the amino group on the benzene ring of procaine. The two ethyl groups on the nitrogen atom of the amino ethanol portion of the procaine molecule are replaced by methyl groups. The molecule of tetracaine conforms to the general configuration characteristics of the "caine" type drugs that have an aromatic nucleus, an ester linkage, an intervening dimethylene chain, and a tertiary nitrogen atom. Shortening the ethyl groups to methyl groups and replacing the hydrogen atom on the amino group with a butyl radical increases the potency and toxicity of tetracaine about 10 times compared to that of procaine (Refs. 1 and 3). Tetracaine manifests topical anesthetic activity both on the mucous membranes and on the skin. The duration of action is approximately 2 to 2.5 times that of procaine because the protein-binding activity and the lipid solubility of tetracaine are increased over those of procaine by the alteration in structural configuration and by the increase in molecular weight (Ref. 3).

Tetracaine is a tertiary amine and, therefore, is a base. It forms salts with various acids including hydrochloric acid. It is generally used as a salt on broken and abraded skin, and as the base on intact skin (Ref. 4). One g of the base dissolves in approximately 1,000 mL of water. Tetracaine base is much more soluble in organic solvents than in water. One g of the base dissolves in 5 mL alcohol, 2 mL chloroform, and 2 mL ether. Tetracaine is less stable than its salts. It is readily soluble in oils and oleaginous bases. The base may be incorporated into water-soluble creams for topical use. It is not as readily released when applied topically from petrolatum bases as it is from water-soluble bases (Ref. 5).

Aqueous solutions of the base decompose rapidly. Tetracaine hydrochloride occurs as fine white crystalline odorless powder and has a slightly bitter taste that is followed by sense of numbness. Solutions of the base are alkaline.

Tetracaine salt solutions can be sterilized by boiling for short periods time. The shelf life is limited to less th 1 year. The shelf life of ointments and other preparations containing the bas is not known (Ref. 3).

(1) *Safety.* Clinical use has confirme that tetracaine is safe in the dosage range used as an OTC external analgesic.

Although tetracaine is sparingly soluble in water, sufficient quantities can be absorbed from extensive areas damaged, abraded, or excoriated skin quantities that produce adverse systemic effects (Ref. 3). High plasma levels of tetracaine will produce convulsions and cardiac depression, a do other local anesthetics of the "cain type. Adriani and Campbell (Ref. 5) have indicated that the cardiovascula reactions may occur without central excitation and cause syncope and cardiac arrest. This type of reaction often occurs abruptly without warning and is usually fatal (Ref. 6). Tetracain is 10 times more toxic than procaine when administered intravenously in animals. Its relative toxicity is equal t that of procaine since 1 mg is equal to mg procaine in potency and toxicity. Due to tetracaine's potency, dosage is more difficult to control and overdosa occurs more readily than with less potent drugs. The intraperitoneal LD_{50} mice is 70 mg/kg. Data on animal toxicity are not in agreement because different methods of studying toxicity different investigators. Rapid intravenous injection into animals irrespective of species causes convulsions and circulatory system depression (Ref. 7).

Differences in results obtained by different investigators are merely quantitative; qualitatively the respons are the same. Tetracaine manifests a greater degree of myocardial depressi than do other drugs of the "caine" typ when the plasma concentrations reach toxic levels (Ref. 6). Tetracaine is hydrolyzed by pseudocholinesterase i the blood, as are procaine and other esters of aminobenzoic acid, but the ra of hydrolysis is approximately one-fift the rate of procaine (Ref. 3). This slow rate of detoxification contributes to th greater degree of toxicity it manifests compared with other drugs of the "caine" type. Tetracaine has no well-defined chronic toxicity. Adverse reactions from repeated use have not

been reported. The action perineurally is reversible and no histological changes have been demonstrated in nerve tissues. The toxic dose in humans is not known. The maximum limit of dosage perineurally or by infiltration is considered to be between 75 to 100 mg in healthy adults. Topically on the mucous membranes of the pharynx, the maximum dose ranges between 25 and 40 mg (Refs. 3 and 6). The toxic dose, when applied externally on the skin, is not known. Tetracaine manifests no appreciable degree of irritancy when the ingredient is injected or applied topically. It may cause the cytotoxic type of reaction after repeated applications (Refs. 3 and 6).

Tetracaine base is safe when applied to limited areas of damaged skin. It is also safe when applied to intact skin because absorption and penetration occur slowly (Ref. 8). Significant amounts of the base are readily absorbed from damaged skin or denuded areas of skin, particularly if such areas are extensive or exceed 25 percent of the total body surface (Ref. 6). Sufficient quantities may be absorbed from damaged skin to produce systemic adverse reactions. Although this has not been reported following the use of tetracaine, it has occurred with others of the "caine" type topical anesthetics. Since tetracaine can act as a haptene, it is capable of producing allergic type reactions mediated by immunoglobulin E (Ref. 3). The sensitizing potential of tetracaine on the skin is no greater than it is with other topical anesthetics. Because tetracaine is a derivative of aminobenzoic acid, the possibility of cross-sensitization is frequently mentioned, but documentation and data substantiating this contention are sparse and not convincing. Cross-sensitization with other derivatives of aminobenzoic acid may occur; but if it does, it is rare (Ref. 3). Tetracaine base penetrates the intact skin (Refs. 4 and 8). Quantities absorbed vary with the area of application. Plasma levels are very low but are detectable by microchemical methods. The Panel does not consider this to be a significant factor in toxic reactions to the drug if the areas of application are limited (Ref. 5). Absorption occurs readily from raw and denuded areas, such as second and third degree burns, and from abraded skin or lesions where considerable area of skin has been injured and an extensive exposed raw surface is present (Ref. 6).

(2) *Effectiveness.* There are studies documenting the effectiveness of tetracaine as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that tetracaine is effective for use as an OTC external analgesic.

Tetracaine penetrates the intact and damaged skin and produces analgesic and antipruritic effects (Refs. 4 and 8). It is absorbed from abraded areas and produces analgesia and anesthesia.

The unionized tetracaine base penetrates and stabilizes the axonal membrane and blocks pain and other receptors in the skin. Tetracaine is much more lipid soluble than procaine and has 10 times the protein-binding capacity of procaine (Ref. 3). Therefore tetracaine has a longer latent period and lasts two to four times longer than procaine. As is the case with other topical anesthetics, the duration of action is variable and depends upon the relative vascularity at the site of application (Ref. 6). Tetracaine base and tetracaine salts are effective topically on the mucous membranes (Ref. 10).

Adriani and Dalili (Refs. 4 and 9) found that tetracaine base was effective in relieving the sensation of burning and itching resulting from electrical stimulation of the skin when a saturated solution in 40 percent alcohol, 10 percent glycerin, and 50 percent water is used. A 2-percent tetracaine hydrochloride solution was totally without effect under similar conditions. Topical preparation to be used on the intact skin for relieving pain, burning, or pruritus should be composed of the base incorporated in a medium which allows a thin film to be present in a moist state continuously over the afflicted areas.

Tetracaine base has been effectively used on intact and damaged skin in concentrations of 1 to 2 percent (Ref. 7).

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 to 2 percent concentration of tetracaine to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly on raw surfaces or blistered areas."

References

(1) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(2) Swinyward, G. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 987–1001, 1970.

(3) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology,* 17:223–242, 1977.

(4) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers, "*Anesthesia and Analgesia,* 50:834–841, 1971.

(5) Adriani, J. and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:527–530, 1956.

(6) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(7) OTC Volume 060047.

(8) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(9) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itch, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(10) Andrews, G. C., "Diseases of the Skin," 6th Ed., W. B. Saunders Co., New York, pp. 107–108, 111, 1971.

aa. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Tetracaine hydrochloride is the salt of the tertiary amine, tetracaine, which has been described above. Tetracaine hydrochloride consists of a white crystalline powder that is oderless and hygroscopic. Tetracaine hydrochloride is soluble, 1 part in 7 parts of water, unlike the base, which is poorly soluble. Tetracaine hydrochloride has a slightly bitter taste that is followed by a sense of numbness. Tetracaine hydrochloride melts at between 147° and 150° C. (Refs. 1 and 2). Tetracaine hydrochloride hydrolyzes slowly and loses its anesthetic activity with time. The shelf life of the powder in sealed ampules is less than 1 year. The hydrochloride is the most widely used salt. Solutions of the salt are more stable than the base and, because they are converted to the base when they are injected or applied topically to the mucous membrances by the buffering mechanisms of the tissues, they are physiologically active and widely used clinically. The salt is not

converted to the base when the salt is applied to the intact skin. For this reason it penetrates very slowly and is without effect (Refs. 3 through 5). Aquesous solutions have a pH of 5 to 6.

(1) *Safety.* Clinical use has confirmed that tetracaine hydrochloride is safe in the dosage range used as an OTC external analgesic.

Tetracaine hydrochloride is 10 times more potent and toxic than procaine (Ref. 1). It may be absorbed in large quantities from abraded and denuded areas because it is water soluble. Tetracaine hydrochloride produces convulsions and cardiac depression similar to those produced by other local anesthetics (Ref. 6). Reactions of this type from topical application to minor skin lesions have not been reported and are unknown. Tetracaine hydrochloride manifests no appreciable degree of irritancy. Sensitizing potential is low but, like all other anesthetics of its type, it will cause allergic reactions. Tetracaine hydrochloride can act as a haptene and cause allergic reactions mediated by IgE immune globulins (Ref. 7). Repeated application can cause the cytotoxic type of sensitization mediated by the T cell lymph system. Topical reactions are characterized by rashes, eczema, etc. (Ref. 8).

(2) *Effectiveness.* There are studies documenting the effectiveness of tetracaine hydrochloride as an OTC external analgesic. Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that tetracaine hydrochloride is effective for use an an OTC external analgesic.

Tetracaine hydrochloride is highly ionized and does not readily penetrate lipid barriers of the cell membrane. Tetracaine hydrochloride is very slowly absorbed from the intact skin and, therefore, exerts no significant therapeutic effect (Refs. 5 and 9). Tetracaine hydrochloride is readily absorbed from abraded skin and open cutaneous lesions. It is effective when it comes into contact with the tissue fluids because it is converted to the base, which is the active form that penetrates the neuronal membrane and blocks conduction of nervous impulses. Absorption from damaged skin occurs readily and systemic reaction can occur if the ingredient is applied over extensive areas of the body (Ref. 6).

Tetracaine hydrochloride has been effectively used on damaged skin in concentrations ranging from 1 to 2 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 1 to 2 percent concentration of tetracaine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervsion of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly on raw surfaces or blistered areas."

References

(1) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(2) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 995–996, 1975.

(3) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 99–106, 1973.

(4) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1183, 1976.

(5) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

(6) Adriani, J., "Absorption and Systemic Toxicity of Local Anesthetics," *General Practitioner,* 25:82–86, 1962.

(7) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology,* 17:223–242, 1977.

(8) OTC Volume 060047.

(9) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

bb. *Tripelennamine hydrochloride.* The Panel concludes that tripelennamine hydrochloride is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient depresses cutaneous sensory receptors and should bear the labeling for topical analgesics, anesthetics, and antipruritics set forth below.

Tripelennamine hydrochloride is 1,2-ethanediamine, *N,N*-dimethyl-*N'*-(phenylmethyl)-*N'*-2-pyridinyl-, monohydrochloride. It may be prepared by the interaction of 2-amino pyridine, 2-dimethylamino ethylchloride, and benzyl chloride. tripelennamine is a derivative of ethylenediamine. It is a base that interacts with acids to form salts. In this respect, it behaves similarly to the nitrogenous type of topical anesthetics. The two salts most commonly used are the hydrochloride and the citrate, which are both white crystalline powders. The citrate is more palatable than the hydrochloride when taken orally. One g of the hydrochloride dissolves in 0.77 mL water, in 6 mL alcohol, in 6 mL chloroform, and is pratically insoluble in benzene, ether, and ethyl acetate. The citrate melts at approximately 106° to 110° C. The hydrochloride melts at 192° to 193.5° C. An aqueous solution of the hydrochloride containing 25 mg/mL has a pH of 6.71 (Refs. 1, 2, and 3).

Tripelennamine hydrochloride slowly darkens on exposure to light. Tripelennamine belongs to the pharmacologic class of antagonists known as the antihistamines. Mirrored in its structure is the configuration common to the topical anesthetic drugs of the "caine" type. However, there is sufficient modification in its structure to attenuate the toxicity characteristic of the "caine" type of topical anesthetics (Refs 4 and 5). In addition to its antihistaminic and topical anesthetic activity, tripelennamine hydrochloride has a weak anticholinergic action (Ref. 6).

(1) *Safety.* Clinical use has confirmed that tripelennamine hydrochloride is safe in the dosage range used as an OTC external analgesic.

Prolonged daily use of tripelennamine causes no untoward effects in the majority of patients on whom it is used topically. No changes in kidney or liver function have been found after prolonged and continued oral use. In a series of 800 patients, only 5.5 percent could not tolerate the drug when administered orally, and required that it be discontinued (Ref. 2).

Adverse effects include drowsiness, dry mouth, nausea, excitement, headache, polyuria, heartburn, loss of potency, diplopia, chilliness, dizziness, sweating, and dysuria. The dry mouth is due to its anticholinergic effect. Performance tests were conducted after a dose of 100 mg tripelennamine administered orally by McKay and Ferguson (Ref. 7), using a complex coordination test and also a rapid calculation test. Results showed impairment of the calculation test but not of the coordination test. Drowsiness proved to be the most sensitive criterion of adverse drug action. Diphenhydramine has a greater tendency to cause drowsiness than tripelennamine but tripelennamine is more spasmogenic on the gastrointestinal and genitourinary tract than diphenhydramine. The incidence of untoward effects using doses ranging from 200 to 300 mg daily is about the same for diphenhydramine as for tripelennamine, but when larger doses are used, the latter is less toxic. Towers and Giuffra (Ref. 8) reported a case of a 39-year-old woman who had taken 6.35 g

over a 4-week interval, 1.35 g of which had been ingested in 48 hours. She complained of dyspnea, pectoral pain, and a burning of the tongue. Cyanosis, rigidity of the entire body, stupor, and circulatory collapse developed. She recovered within 24 hours but had amnesia for 4 days following the episode.

Agranulocytosis has been reported following ingestion of tripelennamine. Tripelennamine hydrochloride was one of the drugs taken by three patients who developed hemolytic anemia following the use of antihistamines over long periods of time (Ref. 9). Other cases of agranulocytosis have been reported. A case of pancytopenia (aplastic anemia) likewise has been reported. A case of purpura has been described (Ref. 10). Gross hematuria and dysuria were frequently described in the early use of the drug. A 32-year-old man who had received 50 mg tripelennamine four times daily for 2 days in the course of treatment for chronic ethmoiditis and prostatitis developed hematuria and dysuria. Impotence has been observed in two patients taking tripelennamine hydrochloride. No cases of systemic toxicity following topical use on the skin have been called to the Panel's attention. Tripelennamine salts and the base are absorbed from damaged skin but not in sufficient quantities to produce systemic adverse effects, unless they are applied to areas exceeding 25 percent of the body surface.

Tripelennamine has a low degree of irritancy and a low sensitizing potential in either base or salt form. The development of acute urticaria, atopic dermatitis, and eczematous contact dermatitis has been reported after topical application in patients who did not have these cutaneous manifestations before topical use. Ellis and Bundick (Ref. 11) found 10 instances of sensitivity to tripelennamine in 141 cases reported. As has been mentioned, the antihistamines are capable of acting as haptenes and producing sensitization mediated by immunoglobulin E (IgE) as well as local cytotoxic reactions due to activity of the T lymphocytic cell system.

The increasing incidence of acquired sensitivity to the antihistaminic creams is discussed by Ellis and Bundick (Ref. 11). These authors indicate that the antipruritic action of topical antihistamine drugs is most useful for 1 to 2 weeks to prevent the continued trauma of scratching and permanent healing. However, loss of efficacy is frequent after uses of 3 to 4 weeks. Sensitivity often develops after this period of use. The Panel does not recommend topical use of tripelennamine or its salts for longer than 7 days except under the advice and supervision of a physician.

(2) *Effectiveness.* There are studies documenting the effectiveness of tripelennamine hydrochloride as an OTC external analgesic.

Tripelennamine was one of the first effective antihistaminic drugs to be adopted for general clinical use in the United States (Ref. 12). Tripelennamine hydrochloride, diphenhydramine hydrochloride, and pyrilamine maleate were found to be the most effective of 13 antihistaminic drugs tested by Sternberg and associated (Ref. 13) for the ability to nullify the effect of histamine in raising wheals in the skin of man in clinical studies.

Tripelennamine hydrochloride is used for the symptomatic treatment of urticaria, hay fever, and other allergic disorders (Ref. 2). It has been reported to be useful in alleviating a variety of cutaneous disorders related indirectly, or not at all, to histamine release (Ref. 2). Tripelennamine prevents the attachment of histamine to the H_1 type receptor on cells. Tripelennamine is effective as an antagonist when histamine is circulating and diffusing extracellularly but is not effective when the histamine is released intracellularly by an antigen-antibody or other type reaction (Ref. 2). In these cases tripelennamine is not protective when used prophylactically or as an antagonist.

Tripelennamine applied by iontophoresis inhibits the wheal formation produced by the intracutaneous injection of histamine or ragweed extract in sensitive persons. The application must be made before injection of the drug. Once the receptor sites are occupied by the histamine, the antihistamine is not effective until the histamine is displaced from the cell (Ref. 2). The antihistamine must be introduced prior to the histamine release. Intracutaneous injections of histamine immediately following the application of 0.5 percent tripelennamine hydrochloride cream to the skin produce the usual reaction; but 5 minutes after the cream is applied, the response is almost completely inhibited. Development of tolerance to continued use of 50 mg tripelennamine hydrochloride three times daily by mouth was observed by Dannenberg and Feinberg (Ref. 14). The response to an intracutaneous dose of histamine was inhibited during the first week. During the second week it produced a minimal effect; and during the third and fourth weeks, it produced a definite wheal (Ref. 15).

Tripelennammine and its salts do not affect or inhibit in any way the antigen-antibody reaction, but they do counteract the local and systemic effects of histamine released by the interaction (Ref. 2). There is considerable evidence that the oral administration of tripelennamine relieves urticaria and other cutaneous reactions, including cases of ivy poisoning and bee stings (Ref. 2). There is evidence that topical creams containing 2 to 3 percent tripelennamine hydrochloride are effective in temporarily relieving the pruritus of poison ivy eruptions. However, it exerts no curative effects. The pruritus of chicken pox has been relieved by oral administration.

Mucosal anesthesia is produced in the oropharynx and rectum by 0.5 to 2.0 percent aqueous solutions of tripelennamine hydrochloride. Solutions of tripelennamine up to 4 percent have been used topically for anesthesia of the mucous membranes in certain dental procedures. The Panel considers this topical anesthetic effect to be significant and partly, if not completely, responsible for its topical antipruritic effect.

As is the case with topical anesthetics, the base of tripelennamine penetrates the intact skin more effectively than do the salts (Refs. 4 and 5). Tripelennamine hydrochloride is absorbed from the damaged skin but there is doubt that quantities sufficient to produce adverse reactions are absorbed from topical applications in localized areas or from lesions causing localized pruritus.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 2.0-percent concentrations of tripelennamine hydrochloride to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1220–1221, 1973.

(2) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1452–1457, 1955.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1249, 1976.

(4) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d

Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(5) Adriani, J. and M. Naraghi, "Pharmacologic Principles of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology*, 17:223–242, 1977.

(6) OTC Volume 060045.

(7) McKay, R. A. and I. K. W. Ferguson, "Influence of Certain Anti-Motion Sickness Drugs on Psychomotor and Mental Performance," *Journal of Aviation Medicine*, 22:194–195, 1951.

(8) Towers, P. A. and L. J. Giuffra, "An Unusual Reaction Following the Use of Pyribenzamine," *New York State Journal of Medicine*, 50:214–215, 1950.

(9) Crumbley, J. J., "Anemia Following Use of Antihistaminic Drugs," *Journal of the American Medical Association*, 143:726–728, 1950.

(10) Uvitsky, L. H., "Purpura Simplex due to Antihistaminic Drugs," *Journal of Allergy*, 22:544–546, 1951.

(11) Ellis, F. A. and W. R. Bundick, "Appraisal of Topical Use of Antihistamines," *Journal of the American Medical Association*, 150:773–776, 1950.

(12) OTC Volume 060068.

(13) Sternberg, T. H., D. J. Perry, and P. LeVan, "Antihistaminic Drugs," *Journal of the American Medical Association*, 142:969–973, 1950.

(14) Dannenberg, T. B. and S. M. Feinberg, "The Development of Tolerance to Antihistamines," *The Journal of Allergy*, 22:330–339, 1951.

(15) OTC Volume 060037.

cc. *Turpentine oil.* The Panel concludes that turpentine oil is safe and effective for use as an OTC external analgesic as specified in the dosage section below. The ingredient stimulates cutaneous sensory receptors and should bear the labeling for topical counterirritants set forth below.

Turpentine oil is commonly misnamed "Turpentine." Turpentine oil for medicinal use must be of better quality than commercial turpentine oil, that is, it should be rectified turpentine oil (Ref. 1).

Turpentine oil is a volatile oil prepared by steam distillation of turpentine oleoresin collected from *Pinus palustrus* and other species of Pinus (Pinaceae) (Ref. 2). It is a colorless liquid having a characteristic odor and taste. Turpentine oil boils at 155° C. It is practically insoluble in water, but is miscible with alcohol, chloroform, and ether. Its chief chemical components are *alpha*- (64 percent) and *beta*-pinene (33 percent) and varying amounts of carene (Refs. 3 and 4).

According to Pirila et al., most oils of turpentine contain large amounts of 2-pinene. However, the 3-carene content varies depending on the country of origin (Ref. 5).

(1) *Safety.* Clinical use has confirmed that turpentine oil is safe in the dosage range used as an OTC external analgesic.

Oral LD_{50} in rats is 1,800 mg/kg (Ref. 6). Several human fatalities from the ingestion of turpentine oil have been reported over the past century, but none from inhalation or topical application. The mean lethal dose orally for adults is approximately 150 mL (Ref. 7). Turpentine oil is absorbed from the intestinal tract and the lungs, and through the intact skin. It is excreted primarily by the kidney (Ref. 8).

Several official formulations contain turpentine oil. These include 25 percent in White Liniment, "British Pharmaceutical Codex" (Ref. 9), 25 percent in Turpentine Liniment, "United States Pharmacopeia" (Ref. 10) and 65 percent in Turpentine Liniment, "British Pharmacopeia" (Ref. 10).

Turpentine oil is both a primary irritant and a sensitizer. As an irritant, it usually acts by defatting the skin, causing dryness and fissuring. It is often used as a cleanser for removing paints and waxes. It is one of the commonest causes of hand eczema.

Turpentine oil is easily oxidized. The oxidized form is more irritating and sensitizing than the fresh product. Cross-sensitization may occur between turpentine and ragweed oleoresin, chrysanthemum, pyrethrum, and various balsams such as those of pine, spruce, and Peru (Ref. 11).

In poisoning due to oral ingestion, turpentine oil may cause hematuria, albuminuria, and coma. The urine has an odor resembling violets. A dose of 140 mL (15 mL in children) may be fatal. The application of liniments containing turpentine oil to the intact skin may cause vesicular eruption, hives, and vomiting in susceptible persons.

Four thousand patients were patch tested in five European clinics with turpentine oil. Positive reactions occurred in 5.2 percent of the males and 6.5 percent of the females tested (Ref. 12).

In a modified repeated-insult patch test, 50 percent turpentine oil caused severe sensitization of the skin (Ref. 13). Patch testing with 10 percent turpentine oil in arachis oil produced positive reactions in 4.3 percent of 1,205 individuals with dermatitis or eczema (Ref. 12).

In a study by Baer, Ramsey, and Biondi (Ref. 14), 540 subjects were patch tested with a solution of 10 percent turpentine oil in olive oil. The intensity of the reaction was rated on a scale of from 1 to 4. Of the 540 subjects tested, 12.2 percent had a positive reaction. Twenty-nine subjects had a rating of 1; 21 subjects had a rating of 2; 16 subjects had a rating of 3, and no subjects had rating of 4 (most intense reaction).

Roe and Field (Ref. 15) conducted studies in which turpentine oil was applied dorsally to the skin of mice af pretreatment with 1,10-dimethyl-1,2-benzanthracene (DMBA). DMBA induces the formation of skin tumors, but generally speaking, not all are carcinomas. After one treatment with DMBA, no further challenge was given for 3 weeks. Two groups of 300 mice were so treated with one group used a a control. The other group was challenged at weekly intervals with 0.2 mL undiluted oil of turpentine applied dorsally to the skin for 33 weeks. Wea tumor promotion occurred with turpentine oil. A total of 10 papillomas was observed in the test group compared with 1 papilloma that appeared outside the treated area in th control group.

Turpentine oil has been used as an ingredient in counterirritant products with a long history of safety. One manufacturer reports sales of more tha 40,000,000 bottles of liniment over a period of 80 years with no reports of customer problems (Ref. 16). Another manufacturer of a liniment containing turpentine oil has been manufacturing and distributing this product since 1913 and reported the manufacture and sale of more than 9,000,000 ounces in 1972. Only two customer complaints alleging injury (minor skin reaction or burn) were received in 1972 (Ref. 17).

The cited clinical studies (Refs. 12 through 14) were performed upon individuals with known histories of dermatological problems. The Panel recognizes the irritant, sensitizing, and tumorigenic potential of turpentine oil, but considers the marketing experience and lack of significant adverse reaction to illustrate the safety of turpentine oil as used in currently marketed OTC dru products.

(2) *Effectiveness.* Due to the ingredient's wide use and clinical acceptance and on the basis of published reports in the literature, the Panel concludes that turpentine oil is effective for use as an OTC external analgesic.

No scientifically controlled studies concerning the use of turpentine oil alone for the treatment of rheumatism, arthritis, and muscular aches and pains were found. However, the use of turpentine oil for self-medication is almost an American folk tradition, and full-strength turpentine oil has been employed with impunity as a topical counterirritant.

Turpentine oil has been effectively used in concentrations ranging from 6 to 50 percent.

(3) *Dosage—For adults and children 2 years of age and older:* Apply a 6 to 50 percent concentration of turpentine oil to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Sollmann, T., "A Manual of Pharmacology and its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 168–169, 1957.

(2) Todd, R. G., "Martindale, The Extra Pharmacopeia," 25th Ed., The Pharmaceutical Press, London, pp. 1467–1468, 1967.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1259, 1976.

(4) Claus, E., V. Tyler, and L. Brady, "Pharmacognosy," 6th Ed., Lea and Febiger, Philadelphia, p. 166, 1970.

(5) Pirila, V., O. Kilpio, A. Olkkonen, L. Pirila, and E. Siltanen, "On the Chemical Nature of Exzematogens in Oil of Turpentine," *Dermatologica,* 139:183–194, 1969.

(6) Sperling, F., H. K. U. Ewenike, and T. Farber, "Changes in LD_{50} of Parathion and Heptachlor Following Turpentine Pretreatment, *Environmental Research,* 5:164–171, 1972.

(7) Gleason, M. M., R. E. Gosselin, H. C. Hodge, and R. P. Smith, "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 315–316, 1976.

(8) Arena, J. M., "Poisoning: Chemistry, Symptoms, Treatments," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 173–174, 597, 1970.

(9) Osol, A. "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1450–1451, 1975.

(10) Osol, A., "The Dispensatory of the United States," 22d Ed., J. B. Lippincott Co., Philadelphia, p. 781, 1940.

(11) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 49–50, 1973.

(12) Bandmann, H. J., C. C. Calnan, E. Cronin, S. Fregert, N. Hjorth, B. Magnusson, H. Maibach, K. E. Malten, C. L. Meneghini, V. Pirila, and D. S. Wilkinson, "Dermatitis from Applied Medicaments," *Archieves of Dermatology,* 106:335–337, 1972.

(13) Klingman, A. M., "The Identification of Contact Allergens by Human Assay," *Journal of Investigative Dermatology,* 47:393–409, 1966.

(14) Baer, R. L., D. L. Ramsey, and E. Biondi, "The Most Common Contact Allergens," *Archives of Dermatology,* 108:74–78, 1973.

(15) Roe, F. I. C. and W. H. Field, "Chronic Toxicity of Essential Oils and Certain Other Products of Natural Origin," *Food and Cosmetic Toxicology,* 3:311–324, 1965.

(16) OTC Volume 060009.

(17) OTC Volume 060040.

Category I Labeling

The Panel was not in agreement with regard to the labeling indications for counterirritant and hydrocortisone products. The Panel, however, was in complete agreement regarding labeling warnings and the labeling indication for analgesic, anesthetic, or antipruritic products. Accordingly, this section consists of a majority report and a minority report for counterirritant and hydrocortisone products. The minority report reflects the opinion of one Panel member.

The majority of the Panel recommends the following Category I labeling for external analgesic active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) *For products containing analgesic, anesthetic, or antipruritic external analgesic active ingredients except for hydrocortisone and hydrocortisone acetate:* "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bits, and minor skin irritations."

(2) *For products containing counterirritant external analgesic active ingredients:* "For the temporary relief of minor aches and pains of muscles and joints, such as simple backache, lumbago, arthritis, neuralgia, strains, bruises, and sprains."

(3) *For products containing hydrocortisone and hydrocortisone acetate:* "For the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

b. *Warnings.* (1) *For products containing any external analgesic active ingredient and hydrocortisone and hydorcortisone acetate:* (i) "For external use only."

(ii) "Avoid contact with the eyes."

(iii) "Discontinue use if condition worsens or if symptoms persist for more than 7 days and consult a physician."

(iv) "Do not use on children under 2 years of age except under the advice and supervision of a physician."

(2) *For products containing counterirritant external analgesic active ingredients:* (i) "Do not apply to wounds or damaged skin."

(ii) "Do not bandage."

c. *Minority report for Category I labeling indications.* The minority of the Panel disagrees with the labeling for Category I indications for topical counterirritant active ingredients and for hydrocortisone and hydrocortisone acetate as topical antipruritic active ingredients recommended by the majority of the Panel. The minority of the Panel recommends that the following Category I indications for the labeling of these active ingredients be generally recognized as safe and effective. A justification for the disagreement with the indications recommended by the majority of the Panel follows each minority recommendation.

(1) *For products containing counterirritant external analgesic active ingredients:* "For the temporary relief of minor aches and pains of muscles and joints."

Because OTC drugs are intended to be used only for the temporary relief of symptoms, the labeling should not indicate or imply that the preparation is for the treatment of a specific disease entity as is the case in the indications recommended by the majority of the Panel, i.e., "For the temporary relief of minor aches and pains of muscles and joints, such as simple backache, lumbago, arthritis, neuralgia, strains, bruises, and sprains." Such indications in the labeling are not amenable to self-diagnosis and self-treatment, and require medical diagnosis and supervision for safe use. Examples of such claims are "arthritis," "neuralgia," and "lumbago."

In addition, the labeling recommended by the majority of the Panel includes claims for bruises, simple backache, strains, and sprains. The majority of the Panel states that "the Panel used the terms in the above list of indications because it believes these terms would be understood by the general population," and that "these are not necessarily terms which would be used by physicians in specific diagnoses." The minority of the Panel disagrees with this assumption because it is contradictory. The terms listed are in fact used by physicians in diagnosing disease processes. The use of dissimilar medical terminology, i.e., the terminology used by physicians and the terminology assumed to be understood by the general population, to designate identical disease conditions would cause consumer confusion and could lead to deception and unsafe use. The use of disease-oriented labeling for symptom-oriented indications may lead to misuse by the consumer. These terms, therefore, are not acceptable for the following reasons:

(i) *Arthritis.* Arthritis is a clinical entity that designates an inflammation of a joint or joints of an arthritic process, and may be of many types and of multivaried etiology. Therefore, it cannot be categorized by one all-inclusive term. Arthritis may be due to trauma, infection, or degenerative changes in the joints. It may be of unknown etiology, such as rheumatoid or osteoarthritis, or it may be a manifestation of a systemic disease, such as rheumatic fever, gout, serum sickness, etc. Self-diagnosis and self-treatment could lead to a delay in proper treatment by a physician and an aggravation of a disease process even to the point of irreversibility. Therefore, the indication for use in arthritis is unacceptable for OTC labeling. However, the labeling recommended by the minority of the Panel, i.e., "For the temporary relief of minor aches and pains of muscles and joints," does not restrict access to a counterirritant analgesic ingredient by a consumer seeking temporary relief of arthritis pain.

(ii) *Neuralgia.* Neuralgia is defined as nerve pain, generally severe, that is throbbing or static in character. It is a medical term designating a clinical entity. Its etiology is unknown, and no histopathologic changes are noted in the afflicted nerve or nerve root. The term is often erroneously used to designate neuritis, which is a medical term that designates a group of clinical conditions of multivaried etiologies that are more aptly described by symptom-oriented labeling than by disease-oriented labeling. Usually, the pain is felt along the course of, or the area of, distribution of the terminal fibers of a nerve. There are various types of neuralgia, designated at times as degenerative, epileptiform (tic douloureux), geniculate, hallucinatory, idiopathic, etc. Neuralgia is generally central in origin. Application of a medicament peripherally would, in many cases, not relieve the symptoms. The term "neuralgia" appearing on OTC labeling again would encourage a consumer to attempt self-diagnosis and self-treatment of a pain which ordinarily is not minor, and is often recurrent and intractable. In certain types of neuralgia, pain can be "triggered" by stimulation of areas referred to as "trigger zones." Counterirritants are stimulants of cutaneous receptors and, if applied to these areas, could aggravate or prolong such types of pain.

(iii) *Lumbago.* Lumbago is a medical term that is defined as an inflammation of the tendinous attachments of the muscles of the lumbar region causing severe pain and rigidity. Pain is felt in the lumbar area. It is also referred to as osphyitis or lumbodynia. Pain along the vertebral column in the lumbar area may be due to many other causes besides tendinous inflammation, such as arthritis of the vertebrae, radiculitis, cord tumor, ruptured intervertebral disks, etc. Pain in the lumbar area may be referred from pelvic viscera, such as the sigmoid colon, uterus, the bladder, prostate, and other intra-abdominal structures. Such a pain may be an early manifestation of disease in these organs. The diagnosis of lumbago, therefore, can only be made by physicians who have the expertise to differentiate lumbago from other clinical entities whose symptoms may simulate the syndrome. The indication "For the temporary relief of minor aches and pains of muscles and joints" does not restrict access by the consumer to an OTC product for the temporary relief of the symptoms associated with lumbago.

(iv) *Bruises.* A bruise is an injury to the skin without breaking its continuity, followed by a discoloration due to the formation of a hematoma and extravasation of blood at the site of the trauma. It is usually caused by blunt traumas. It is usually superficial but may at times be deep. Superficial bruises occur in the skin and are not necessarily painful. "Deep" bruises involve the subcutaneous tissue and even muscles. Deep bruises may be accompanied by edema and hematomas in subcutaneous structures beneath the discoloration. The term "bruise" is, at times, used interchangeably with the term contusion. Areas of discoloration of the skin due to extravasation of blood, referred to as ecchymosis, may occur spontaneously and be due to vascular injury or deficiencies or abnormalities of clotting mechanisms. Since counterirritants are vasodilators and can act both locally and centrally as vasodilators, their use on a bruise may actually be contraindicated because they may aggravate the condition.

(v) *Sprains.* A sprain is an injury to a joint with possible rupture of some of the ligaments or tendons, but without dislocation or fracture. The word "sprain" should not be included in the indication of the labeling of an OTC product intended for counterirritation for the relief of minor aches and pains of muscles, joints, and tendons. It would encourage self-diagnosis and self-treatment by the consumer. The differential diagnosis between a fracture and a sprain is not easily made. A fracture is often overlooked and called a sprain. Furthermore, both fractures and sprains require immobilization and are best treated in this manner. The application of a counterirritant to the injured area would temporarily relieve the symptoms and cause the subject to continue activity and possibly further aggravate the injury.

(vi) *Strains.* A strain is a term used to designate overuse of a part of the body, generally a muscle. It is vague, not specific, and can mean different things to different persons and therefore be misleading to a lay consumer. Besides, it encourages self-diagnosis and self-treatment. An ache or a pain developing in a joint or muscle could be a warning of an incipient, serious disease process. Overuse of a muscle or joint does not ordinarily cause pain if there has been no trauma. If overuse does cause pain, such a pain or ache is self-limiting and disappears after rest; furthermore, the label indication for "the temporary relief of pain of muscles and joints" does not preclude the availability of the product for use in "sprains."

(vii) *Simple backache.* "Simple backache" is an undesirable term that is vague and nonspecific and that can have different meanings to different persons. Backache is a general term that neither describes the exact nature or location nor gives any clue as to the severity of the ache, whether it is deep or superficial, or whether it involves the sacrum or lumbar vertebrae or both. Placing the adjective "simple" before the term is misleading. There is no such thing as "simple stomach ache"; likewise, the adjective "simple" applied to backache is misleading. Backache may, like lumbago, mean many things and be due to a variety of causes. Use of the terms "backache" or "simple backache" would encourage self-diagnosis and self-treatment by a consumer.

(2) *For products containing hydrocortisone and hydrocortisone acetate as topical antipruritic active ingredients:* "For the temporary relief of minor skin irritations and itching."

Because OTC products containing hydrocortisone preparations are intended to be used to relieve symptoms, labeling that includes a list of clinical entities or pathologic states encourages self-diagnosis and self-medication. Such clinical entities require diagnosis and treatment by a physician. Therefore, the indications on the labeling recommended by the majority are unacceptable and would not protect the consumer, i.e., "For the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas." Rashes due to

"eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, and jewelry" are unacceptable additions for the following reasons:

(i) *Eczema.* The term "eczema" refers to an inflammation of the skin and also describes a clinical entity that has multivaried etiologies. There are many manifestations of eczema, and the disease entity varies in severity and distribution. In addition, it simulates cutaneous lesions due to specific causes, such as lesions due to psoriasis, and other multivaried dermatologic diseases. Its use in the indication section of the labeling for hydrocortisone and hydrocortisone acetate preparations would encourage the consumer to self-diagnose and self-treat. The diagnosis of eczema must be made and the treatment directed by a physician. Eczema is not necessarily a transient and self-limiting affliction of brief duration, but one which can be acute, progressive, and sometimes protracted. It may recur, after receding temporarily, after the application of a steroid. The term, therefore, should be deleted from the labeling proposed by the majority of the Panel.

(ii) *Dermatitis.* Dermatitis is a general medical term used to designate an inflammatory condition of the skin. Dermatitis also may have multivaried etiologies. It may be due to an infection, to some exogenous or endogenous agent that produces primary direct irritation, or irritation due to local sensitization of an immunogenetic type (contact allergic dermatitis).

The term "dermatitis" is objectionable for the same general reasons given above for the term "eczema."

The minority of the Panel could also enumerate in detail similar objections for the inclusion of the terms "poison ivy," "poison oak," "poison sumac," "soaps," "detergents," and "jewelry" as it has for "eczema."

The majority of the Panel includes in the labeling of hydrocortisone and hydrocortisone acetate "itchy genital and anal areas." The term "anal areas" indicates that the preparation may be applied at a mucocutaneous junction. The absorption of topical preparations from the skin differs from the absorption from mucous membranes, such as are found at mucocutaneous junctions. The same is the case if the itching involves femal genitalia, such as the vulva. The majority of the Panel does not specify the area of involvement. The pharmacokinetics of the absorption of externally applied topical analgesics differs from the absorption of internally applied topical analgesics. Steroids are readily absorbed from the mucous membranes, and greater blood levels may be obtained than from the application of steroids to the skin. Furthermore, lesions at these anatomic sites do not come under the purview of this Panel.

Hydrocortisone and related steroids relieve the symptoms of, or temporarily arrest the progress of, many systemic and skin diseases whose etiologies are unknown. Therefore, the Panel minority does not consider indication labeling that is disease-oriented appropriate for hydrocortisone and hydrocortisone acetate.

The labeling for hydrocortisone as recommended by the minority of the Panel, "For the temporary relief of minor skin irritations and itching," in no way restricts a manufacturer from making available a product for the temporary relief of the symptoms of the various clinical entities that have been listed in the indications on the labeling recommended by the majority of the Panel.

In summary, the minority of the Panel emphasizes that external analgesics may relieve the pain and itching due to various physical conditions and cutaneous lesions. A comprehensive list of the sites of various kinds of lesions or the sites of pain or discomfort would be lengthy. Such a list would not only confuse and mislead the consumer but would also imply that the product treats the physical condition, lesion, or disease instead of temporarily relieving the pain (symptom) and discomfort associated with the physical condition, lesion, or disease, and would encourage self-diagnosis and self-treatment.

The minority of the Panel also emphasizes that the recognition of a dual medical terminology, i.e., a terminology that is assumed will be understood by the consumer and a terminology that is properly used in diagnoses by physicians, is irrational and unrealistic. The use of a terminology that is assumed will be understood by the consumer is inappropriate for OTC labeling, which should contain only symptom-oriented indications and not disease-oriented indications.

The minority of the Panel concurs with the conclusion of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products published in the **Federal Register** of July 8, 1977 (42 FR 35346) that the use of only a partial list of claims, such as "arthritis," "neuralgia," "lumbago," "eczema," "dermatitis," etc., in the labeling of a product would mislead the user into believing the preparations treat these particular disease conditions as distinguished from other disease conditions. Therefore, the minority of the Panel urges the following: that the disease conditions and cutaneous lesions in the indications for topical counterirritant active ingredients, and for hydrocortisone and hydrocortisone acetate as topical antipruritic active ingredients, recommended by the majority of the Panel be deleted; and that the Category I indications recommended by the minority of the Panel be adopted by FDA.

2. *Category II conditions under which external analgesic active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from external analgesic drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

The Panel has classified the following external analgesic active ingredient as not generally recognized as safe and effective:

Chloral hydrate. The Panel concludes that chloral hydrate is safe but not effective for use as an OTC external analgesic.

Chloral hydrate was discovered in 1832 by Liebig, but it was not used in medicine as a hypnotic until 1869 (Ref. 1). The terms "chloral" and "chloral hydrate" are often used interchangeably but there is a difference between them, because chemically and physically they are two distinct compounds. Chloral is trichloracetaldehyde, while chloral hydrate is chloral that has interacted with one molecule of water. This causes a modification in structure and converts it to a dihydric alcohol. The water interacts with the aldehyde group of chloral. Thus, in chloral hydrate, the unhalogenated carbon has two hydroxyl groups. In addition, another molecule combines with the hydrate as water of crystallization. Its impiric formula, therefore, is $CCl_3CH(OH)_2 \cdot H_2O$ rather than $CCl_3C(OH)_2$. Chloral is a liquid, while the chloral hydrate is a crystalline powder composed of white crystals. Chloral hydrate has an aromatic, penetrating, and slightly acrid odor. It is slightly bitter and has a caustic taste. When exposed to air or when warmed, it slowly volatilizes to chloral. The crystals have a low melting point of 57°C. The resulting liquid boils at 98° C. Heating causes dissociation of chloral hydrate to chloral and water. Both chloral and chloral hydrate are freely soluble in water. One g of chloral hydrate dissolves in 0.25 ml water, 1.3 ml alcohol, 2 ml chloroform, and 1.5 ml ether. It is also soluble in glycerin, acetone, and various glycols. It is very soluble in vegetable oils and freely soluble in turpentine (Ref. 1 and 2).

Aqueous solutions of chloral hydrate are not stable and are quickly decomposed by light, heat, or air to hydorchloric acid, trichloroacetic acid,

and formic acid. Under ordinary conditions of storage, chloral hydrate solutions decompose very slowly. Aqueous solutions of chloral hydrate may develop molds. Therefore, such solutions should not be kept for long periods of time without a preservative. Chloral hydrate is incompatible with iodides, cyanides, permanganates, boraxate, borax, and alkalis, such as the hydroxides. It is also incompatible with carbonates, bicarbonates, lead acetate, camphor, quinine, theobromide, sodium phosphate, urea, urethane and phenacetin (Refs. 1 and 2).

Chloral combines with alcohol to form chloral alcoholate, which systemically is less effective as a hypnotic and sedative than chloral. Chloral condenses with numerous compounds to form derivatives from which chloral is released when they are used therapeutically. Among these are chloral ammonia, chloral antipyrine, chloral formaldehyde, etc. Chloral combines with sugars to form chloralose, which is used as an anesthetic in laboratory animals. In aqueous solutions, chloral and chloral hydrate are incompatible with alkalis that cause decomposition with the formation of chloroform and a formate. This reaction occurs also when chloral hydrate is combined with sodium derivatives of barbiturates that are alkaline (Ref. 3).

(1) *Safety.* Chloral hydrate is a hypnotic and sedative when ingested orally. Some clinicians consider it to be one of the best sedatives available, even though it is not used as extensively as it was before the introduction of barbiturates and other sedatives. It is used chiefly for insominia, but also in patients undergoing morphine or alcohol withdrawal, or in patients with delirium tremens. As is the case with most hypnotics, it is a poor analgesic and will not control pain in oridnary therapeutic doses. Systemically, it depresses the central nervous system, dulling both sensory and motor functions of the brain. Poisoning, after oral ingestion, is characterized by deep coma. The clinical findings in chloral hydrate poisoning are an initial delirium stage, followed by a deepening sleep, and then coma. The pupils first contract and then dilate. The respiratory rate and minute volume exchange decrease, and respiratory arrest follows. The pulse weakens, decreasing at first, but later may become rapid and irregular. The body temperature falls, the muscles relax, and sensibility and reflex action are diminished or completely abolished. In most cases, the immediate cause of death is respiratory failure but a simultaneous cardiac arrest seems to occur in others.

The Panel concludes that an elaborate and detailed discussion of the animal and human toxicology of chloral hydrate is superfluous because the drug has been widely used for many years, its pharmacologic internal effects have been extensively studied, and its safety established. When taken internally, chloral and chloral hydrate are reduced to trichloroethanol, which is conjugated with glucuronic acid in the liver in the detoxification process. The oral dose ranges from 0.5 to 1.0 g every 4 to 6 hours. Because the therapeutic does is relatively large, the Panel doubts that toxic doses would be absorbed from the skin in adults.

Chloral hydrate is somewhat irritating to the skin and mucous membranes. It is not caustic, nor is it a vesicant. Its alleged irritating effect accounts for its past used as a rubefacient (counterirritant) in liniments. One compound is a complex known as camphorated chloral, which results when camphor and chloral interact. How much of the counterirritating effect is due to camphor cannot be stated. Patients ingesting chloral hydrate for systemic use often experience gastric distress, nausea, and vomiting, particularly when the drug is taken on an empty stomach or in concentrated form. This irritating effect is transient and is greater on the mucous membranes than on the skin.

Systemically, chloral hydrate has a potential for causing dependency. In many respects, dependent individuals have the same manifestations as those who are dependent on alcohol. Withdrawal symptoms occur that are difficult to distinguish from the alcohol abstinence syndrome (delirium tremens). Chloral hydrate is a restricted substance subject to the control of the Drug Enforcement Agency for systemic use. Occasionally, chloral hydrate will produce skin lesions, but the local sensitizing and allergenic potential of the skin following topical applications is low. Allergic reactions are uncommon. Prolonged use by the oral route may cause hepatitis, similar to that observed with chloroform. This has not been reported from its topical use on the skin.

(2) *Effectiveness.* The Panel concludes that chloral hydrate is not effective for use as an OTC external analgesic.

The systemic effects of chloral hydrate and its derivatives are undisputed, but its topical analgesic effectiveness is questionable. Although it was used years ago as a topical analgesic, it is no longer recommended in official compendia for this purpose. There is no evidence to indicate that it has a topical anesthetic action even though it is an alcohol. This may be due to its being a dihydric alcohol, which is not as effective as a monohydric alcohol in topical anesthetic action. Chloral hydrate does not block nerve conduction as do the topical anesthetics. However, it has been used in some preparations for topical application as a counterirritant. Chloral hydrate is alleged to be irritating to the skin and mucous membranes, which accounts for its past use as a rubefacient (counterirritant) in liniments. The topical irritation applies to the mucous membranes also. However, it is questionable whether it is as effective and stable as other available compounds (Ref. 1).

After careful review of the data available for chloral hydrate, the Panel concludes that the ingredient is not effective as an external analgesic.

(3) *Evaluation.* The Panel concludes that chloral hydrate is not effective for use as an OTC external analgesic because it does not block nerve conduction as do the topical anesthetics.

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 271–272, 1973.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 260, 1976.

(3) Adriani, J., "Halogenated Compounds," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 325–327, 1975.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of the product is unsupported by scientific data and in some instances by sound theoretical reasoning. The Panel was not in agreement with regard to Category II claims requiring the diagnosis and care of a physician. It was, however, in complete agreement regarding all other Category II claims. Accordingly, this section consists of a majority and a minority report identified below on claims requiring the diagnosis of a physician. The minority report reflects the opinion of one member of the Panel.

The Panel considers the following claims to be misleading or unsupported by scientific data:

a. *Claims related to product performance.* The Panel has considered the following claims related to the performance of a product and considers them to be confusing, meaningless, and misleading to the consumer, and has therefore classified them as Category II: "fast," "swift," "sudden," "immediate," "prompt," "poignant," "bright," "fast cooling pain relief," "relief of cuts,

scratches, abrasions, wounds, etc.," "rubs out pain fast," "diminishes swelling," and "stops pain."

b. *Claims requiring the diagnosis and care of a physician*—(1) *Majority recommendation.* These claims are not amenable to self-diagnosis and self-treatment and require medical diagnosis and supervision for safe use. Examples of such claims are "rheumatic . . . aches," "bursitis," and "rheumatism."

c. *Minority recommendation.* These claims are not amenable to self-diagnosis and self-treatment and require medical diagnosis and supervision for safe use. Examples of such claims are "rheumatic . . . aches," "arthritis," "bursitis," "neuralgia," "bruises," "simple neuralgia," "sprains," "lumbago backache," "rheumatism," and "rashes due to poison ivy, poison oak, poison sumac, eczema, dermatitis, soaps, detergents, cosmetics, and jewelry, and itchy genital and anal areas."

d. *Pharmacologic activities not considered by this Panel and considered by other Panels.* Some claims on the labeling of external analgesic products refer to pharmacologic activities of drugs that were not considered by the Panel. These claims contain pharmacologic activities that do not pertain to the pharmacologic activities of ingredients used as topical analgesics, topical anesthetics, topical antipruritics, or topical counterirritants. Examples of these claims are "fungistatic for athlete's foot," "kills germs," "antiseptic," "discourages infection," "helps prevent infection," and "first aid."

e. *Claims containing anatomical areas specifically considered as deferred to other Advisory Review Panels.* Some Advisory Review Panels have been charged with the evaluation of ingredients for OTC use on specific anatomical areas, e.g., the Advisory Review Panel on OTC Hemorrhoidal Products. Claims referring to such anatomical areas have been deferred because they will be considered by the appropriate Advisory Review Panel. These include such claims as "pain due to hemorrhoids," "relief of athlete's foot," "piles," "diaper rash," and "denture irritation."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 3 years be permitted for the completion of studies to support the movement of the following Category III conditions to Category I: effectiveness for the ingredients aspirin, glycol salicylate, salicylamide, triethanolamine salicylate, and thymol, and the claim for relief of deep seated pain for any ingredient. The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of all other Category III conditions to Category I.

Category III Active Ingredients

Aspirin
Camphorated metacresol
Chlorobutanol
Cyclomethycaine sulfate
Eucalyptus oil
Eugenol
Glycol salicylate
Hexylresorcinol
Salicylamide
Thymol
Triethanolamine salicylate

a. *Aspirin.* The Panel concludes that aspirin is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetic, and antipruritics.

Aspirin is the acetyl ester of salicylic acid (acetylsalicylic acid) (Ref. 1). Acetylsalicylic acid had been synthesized some years before it was introduced into medicine by Dreser in 1899. It was first known as acetyl spiricum, from which the name aspirin is derived. Originally it was obtained from a plant source, *Spiraea ulmaria.*

Aspirin is an ester of salicylic acid. The acetic acid interacts with the hydroxyl group on the 2 position of salicylic acid. Aspirin is a powder consisting of white, tubular, or needle-like crystals. It is odorless and somewhat bitter tasting. Aspirin melts at approximately 135° C. In moist air it slowly hydrolyzes to salicylic and acetic acids and acquires the odor of acetic acid. The decomposition may be retarded somewhat by glycerin (Ref. 2). One g dissolves in approximately 300 ml water, 5 ml alcohol, 17 ml chloroform, and 10 to 15 ml ether. Two polymorphic forms have been described. One form is prepared in a slow crystallization process at room temperature from a saturated solution of aspirin in 95 percent alcohol. This form melts at between 143° and 144° C. The other is obtained simply from evaporation of hexane solution. It melts at between 123° and 125° C. Tablets prepared from the product derived from the slow crystallization technique have a slower rate of dissolution than tablets prepared from the hexane solution. Some evidence suggests that both forms of aspirin crystals are converted to the less soluble form during dissolution. Study of aspirin in aqueous media has led to the suggestion that a phase change occurs on the surface of the crystals (Ref. 1).

Aspirin readily undergoes hydrolysis in aqueous solutions with the liberation of salicylic and acetic acids. In pure water, complete decomposition takes place in 100 days. Acids hasten the rapidity of hydrolysis. The alkalis present in solutions of alkaline acetate and citrate dissolve aspirin, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Half the aspirin decomposes in about 4 days. The decomposition may be retarded somewhat by glycerin and sugar. Liquefaction occurs when aspirin is saturated with phenyl salicylate, acetanilid, phenacetin, aminopyrine, antipyrine, and many other organic products. Partial hydrolysis occurs in mixtures of aspirin and hydroscopic substances or salts containing water of hydration. Even some talcs adversely affect the stability of aspirin (Ref. 3).

(1) *Safety.* Clinical use has confirmed that aspirin is safe in the dosage range used as an OTC external analgesic. When aspirin is applied topically to the skin, it is neither an irritant nor a counterirritant. Aspirin is both an ester and a weak acid. The acid id poorly ionized to the acetylsalicylate ion and the hydrogen ion in aqueous solution. Following oral ingestion it is absorbed from the stomach in the nonionized form. It is more highly ionized in the small intestines, and is absorbed as acetylsalicylate ion. Peak serum levels are reached in 1 to 2 hours after oral ingestion. Half or more of the aspirin circulating in the blood is bound to plasma proteins, especially albumin. The drug is very rapidly distributed to all highly perfused, watery body tissues. Since it has a short half-life, it is excreted very rapidly, largely in the urine. Most of it is excreted within a few hours, although traces continue to be excreted for several days. However, larger doses of aspirin do not follow first-order kinetics, and the higher the dose, the longer the half-life (Ref. 4). In febrile patients, a portion of the drug excreted is eliminated unchanged, but most of it is converted to salicyluric acid. Smaller amounts are eliminated as salicylic acid. It also conjugates with glucuronic acid in the liver to form glucuronates which are excreted in the urine. Some is eliminated as gentisic acid (Ref. 5).

Aspirin is not highly toxic, notwithstanding the voluminous literature on poisoning by the drug. Much of the poisoning is accidental and occurs in children. Poisoning in adults is uncommon. When the widespread use of aspirin is taken into consideration, the

total number of cases of poisoning that have occurred is small when extrapolated to the number of doses used.

A single dose of 10 to 30 g aspirin may be fatal, although survival has been reported when much larger doses have been ingested. Deaths from smaller doses have been reported. Impaired renal function interferes with excretion and accentuates toxicity. A total of 12 g ingested during 24 hours usually produces symptoms of salicylism, such as tinnitus, vertigo, impaired hearing, and headache. More severe manifestations include hyperpnea, fever, metabolic acidosis, and, less regularly, dimness of vision, sweating, thirst, vomiting, diarrhea, skin rashes, tachycardia, restlessness, and delirium. Salicylism may resemble diabetic and renal disorders. Central nervous system depression, stupor, coma, cardiovascular collapse, convulsions, and respiratory failure may be part of the clinical picture of salicylism. Fatal cases show diffuse changes in endothelial tissues with petechial hemorrhages and congestion throughout the viscera (Ref. 5).

The esters and other derivatives of salicylic acid may have an adverse effect upon the clotting mechanism. Aspirin is known to inhibit prothrombin formation, prolong prothrombin time, and interfere with the action of platelets on the clotting mechanisms. Even slight traces circulating in the blood can exert an adverse effect on the activity of platelets that lasts several days. Although salicylates are absorbed from the skin and detectable blood levels result from this absoption, the Panel believes that a special warning regarding possible adverse effects of topically applied esters of salicylic acid is not necessary (Refs. 5 and 6).

One of the untoward effects following oral administration of undissolved aspirin is gastrointestinal bleeding. The extent of blood loss is dose related. The effect that reportedly occurs in 70 percent of patients taking repeated doses of aspirin has been studied by determining the fecal blood loss in healthy human volunteers injected with radioactive chromium-51 tagged red blood cells. The radioactivity of the stools provided a measure for blood loss. During the drug-free control period, the average daily blood loss in one group of volunteers was 0.3 mL per individual. With doses of aspirin of 2.6 g daily, the average loss was increased to 2.3 mL per individual. When doses of 4.5 g aspirin were administered daily, losses increased to 6 mL per individual (Ref. 7).

Because the administration of aspirin in these subjects caused an increase in bleeding time from an average of 2.6 minutes during the control period to an average of 4.5 minutes when aspirin was given to them, the question of whether gastrointestinal bleeding is due to the local effect on the stomach mucosa or to a systemic effect related to the prolonged bleeding time has been the subject of considerable debate.

When aspirin as a sodium salt is injected intravenously, gastric intestinal bleeding does not occur, implying that bleeding is due to a local effect. Bleeding time is prolonged to approximately the same degree whether aspirin is given orally or parenterally. The importance of recognizing this untoward effect of aspirin in patients with hemostatic abnormalities and clotting defects has been stressed and documented in many reports. Although the prolongation of bleeding time has been ascribed by some clinicians to a defective vascular response, others attribute it to a decrease in blood platelet aggregation. Following injury to a capillary, endogenous adenosine diphosphate is released from platelets, causing an irreversible aggregation which results in the formation of a plug in a capillary that is primarily responsible for the arrest of bleeding. Aspirin apparently inhibits the release of endogenous adenosine diphosphate and thereby prolongs bleeding time. As little as 5 gr aspirin can produce this type of abnormal platelet response, and the abnormality persists anywhere from 4 to 7 days, corresponding to the lifespan of the platelets. Because aspirin is absorbed in appreciable amounts through the skin and circulates in the blood, the effect it may have upon coagulation is important in patients whose clotting mechanism is disturbed (Ref. 8).

Idiosyncrasy to aspirin is rare. But aspirin may cause hypersensitivity reactions. These reactions are of two types: a nonimmunogenic reaction characterized by the triad of hypersensitivity, nasal polyps, and asthma; and an immunogenic reaction that occurs in atopic individuals. The nonatopic reaction is probably related to the inhibition of prostaglandin synthesis. As is the case with any other drug, aspirin can act as a haptene and produce an immunogenic type of sensitization. Sensitization is most frequently observed in high risk allergic atopic individuals, particularly in asthmatics and individuals with nasal polyps (Refs. 9 and 10). The manifestations of an allergic response are urticaria, erythema, desquamated bullous or purpural skin lesions, angioneuronic edema, laryngeal stridor, asthma, and peripheral vascular collapse. Absorption of aspirin from damaged skin may produce a systemic allergic response. These reactions are often serious and can be fatal. Direct application of aspirin to the skin may produce irritation in susceptible individuals, but this is uncommon. Large doses of aspirin reduce plasma prothrombin levels in subjects with nonbleeding problems and hence increase prothrombin time, but this effect is clinically significant only when anticoagulants are administered.

The Panel concludes from the ingredient's extensive oral use and long marketing history that aspirin is safe when used topically, and that even though it is readily absorbed through the skin, the risk-to-benefit ratio is low. Aspirin has a relatively low incidence of serious toxic effects associated with short-term use for the majority of the target population. Toxic reactions due to the application of overdoses to the skin are unknown. However, the Panel emphasizes that this does not mean that aspirin circulating in the blood after percutaneous absorption has no adverse effects.

(2) *Effectiveness.* Aspirin is the most widely used OTC internal analgesic ingredient in the United States (Ref. 11). In view of its immense popularity in this country, it has been extensively discussed in the medical and scientific literature. Aspirin is useful to relieve mild to moderate pain, not only when the pain is localized but also when it is generalized. Thousands of articles have been written concerning the safety and effectiveness of aspirin since the first pharmacologic data were reported in the literature in 1899.

Aspirin possesses no direct topical anesthetic activity and does not block the neuronal membrances as do the topical anesthetics such as benzocaine, tetracaine, lidocaine, etc. Therefore, it exerts no anesthetic, analgesic, or antipruritic effect on the skin. Some degree of percutaneous absorption of salicylate esters occurs through the intact skin (Refs. 12 and 13), but no significant cutaneous analgesic or anesthetic activity has been demonstrated. Kionka (Ref. 14) states that, of all salicylates, aspirin is the best absorbed percutaneously from various types of solution, and that the percutaneous absorption of aspirin is increased 30 percent when 2 percent camphor is present. In another statement attributed to Fantus (Ref. 14), it is said that absorption of salicylates through the skin is increased if the solution contains 20 percent alcohol. Blood levels of salicylates have been

demonstrated after cutaneous application using tracer elements in animals. Excretion of salicylates and metabolites into the urine has been demonstrated after percutaneous absorption. Comparisons of blood levels following topical application to those following oral ingestion of therapeutic doses have not been made. Claims have been made that localized areas of myalgia and other painful muscular skeletal disorders are relieved by the applciation of esters of salicylic acid to the affected part. Data to support the contention that this is due to a local action of the ingredient are lacking.

The Panel concludes from available data that the action of salicylates is systemic and that any analgesic effect resulting from topical application is due to the blood-borne drug distributed systemically in the same manner it would be after oral absorption. The exact mechanism by which salicylates produce their analgesic effects is not known, but it is generally conceded that they act in part by exerting an anti-inflammatory effect and in part by a central depressant effect. Systemic salicylates also exert a peripheral anti-inflammatory action. Some workers have attempted to explain the action of salicylates on the basis of their effects on the water balance of tissues. In addition, there is considerable evidence that aspirin interferes with the synthesis of prostaglandins and exerts its analgesic effect in this manner. Although the Panel accepts the fact that aspirin may have a dual effect, that is, one acting centrally and one peripherally, it does not support the assumption that the drug penetrates the skin and passes into and exerts its effect on the structures beneath and skin. The Panel finds no evidence to support the fact that salicylates, including aspirin, produce an antipruritic or analgesic effect within the skin. The Panel does not disagree that the blood-borne drug may exert an effect on the musculo-skeletal structures and relieve pain if the drug is absorbed in sufficient quantities to produce effective plasma levels. However, the Panel has insufficient evidence to support this contention.

Although 5 to 6 percent concentrations of aspirin have been used topically in OTC preparations, there is insufficient evidence to support the contention that such concentrations are effective.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 5 to 6 percent concentration of aspirin to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use this product if you are allergic to aspirin."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 160–164, 1973.

(2) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 15, 1955.

(3) Gold, G. and J. A. Campbell, "Effect of Selected U.S.P. Talcs on Acetylsalicylic Acid Stability in Tablets," *Journal of Pharmaceutical Sciences,* 53:52–54, 1964.

(4) Levine, R. R., "Pharmacology: Drug Actions and Reactions," Little, Brown, and Co., Boston, pp. 211–218, 1973.

(5) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, pp. 326–339, 1975.

(6) Quick, A. J., "The Story of Salicylates in Bleeding Problems in Clinical Medicine," W. B. Saunders Co., Philadelphia, pp. 14–33, 1970.

(7) Leonards, J. R. and G. Levy, "Soluble Buffered Aspirin Sought to Eliminate Blood Loss in the Stomach," *Journal of the American Medical Association,* 209:17–19, 1969.

(8) O'Brien, J. R., "Aspirin and Platelet Aggregation, *Lancet,* 1:204–205, 1968.

(9) Speer, F., "Aspirin Allergy: A Clinical Study," *Southern Medical Journal,* 68:314–318, 1975.

(10) Fein, B. T., "Aspirin Shock Associated with Asthma and Nasal Polyps," *Annals of Allergy,* 29:598–601, 1971.

(11) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 99–106, 1973.

(12) Beutner, R., et al., "On the Absorption and Excretion of Methylsalicylate Administered by Inunction," *Journal of Laboratory and Clinical Medicine,* 28:1655–63, 1943.

(13) Greiner, H., "Klinischer Erfahrungsbericht uber ein neues perkutan wirkendes Antirheumatikum," *Medizinische Welt,* 48: 2667–9, 1968.

(14) OTC Volume 060008.

b. *Camphorated metacresol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of camphorated metacresol for use as an OTC external analgesic. During the testing period provided to demonstrate safety and effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Camphorated metacresol is either a "complex" formed by the interaction of camphor with metacresol or a solution of the cresol in camphor. Whether a definite chemical complex forms or whether the cresol dissolves in the camphor has not been established. It is claimed (Ref. 1) that cresol is released in small quantities from the complex to exert its therapeutic effect. The amount of camphor that combines with the cresol is approximately 66 percent on a weight-for-weight basis. The amount of metacresol is approximately 22 percent on a weight-for-weight basis. Camphorated metacresol has been on the market since 1930. No other data on the chemical and physical properties of the combination of the two ingredients were supplied to the Panel (Ref. 1).

Phenol combines with camphor to form a complex. This results in a marked decrease in the caustic action of phenol. Because metacresol is a phenol, it has been assumed that with camphor it also forms a similar complex that results in a decrease in caustic action. No data have been supplied, nor has the Panel found any data in the medical literature to support these assumptions. The assumption of the supposed effectiveness of camphorated metacresol is based on the fact that a phenol-camphor complex is effective, and is not based on any laboratory or clinical data (Ref. 1). The three forms of cresols are ortho, para, and metacresol. Of these, the metacresol is less toxic than phenol (Ref. 2).

(1) *Safety.* Data on the clinical use as an OTC external analgesic are insufficient to conform that camphorated metacresol is safe.

There were two reports of adverse reactions (Ref. 1). Both were caused by accidental swallowing of the liquid. One report concerned a child who reportedly swallowed ½ ounce metacresol. The child developed convulsions shortly after ingestion. The patient rapidly improved after several hours and was discharged from the hospital the day after the incident occurred. The second case involved a woman who, as a hospital patient, swallowed an undetermined amount of the preparation. A tablespoonful of epsom salts dissolved in water was administered orally and the stomach was pumped. The patient recovered. The woman suffered no post-ingestion sequelae. Other than these two reports, there have been no indications that this compound has caused any harm to

humans. These were cases that resulted from accidental use or misuse of the product. No fatalities have been reported (Ref. 1). The Panel stresses that it found no other data concerning this product in the textbooks and medical literature that were reviewed.

Data on animal and human toxicity was not provided in a submission to the Panel. It has been claimed that camphorated metacresol causes no irritancy to the skin. However, this claim is based on uncontrolled patch tests in rats.

When this cresol complex is applied topically, the index of its caustic effects on the skin is alleged to depend on the amount of free cresol released from the camphor complex. For instance, in a ratio of 3:1 camphor-metacresol, a 25-percent cresol preparation releases approximately 2 percent free metacresol. This, it is claimed, is a noncaustic level on the skin. Data substantiating this statement are lacking. At the ratio of 3:2 camphor-metacresol (40 percent cresol), the free metacresol level rises to 8 percent and at a 1:1 ratio of camphor-metacresol, the level of free cresol increases above 16 percent.

In combination with camphor, cresols are released slowly if there is no water present. Water causes the cresol to be released more rapidly and in quantities greater than those mentioned above. Since tissues are composed of water, the Panel is deeply concerned that application of this preparation to the skin, particularly if open lesions are present, may cause caustic quantities of cresol to be released.

Based on the lack of sufficient data on systemic and topical toxicity in animals and in man, the Panel concludes that camphorated metacresol must be classified as Category III at this time.

(2) *Effectiveness.* The Panel concludes that the data are insufficient to classify camphorated metacresol as effective for use as an OTC external analgesic.

The panel has found no information documenting the effectiveness of camphorated metacresol as a topical analgesic, anesthetic, or antipruritic in textbooks and other literature that was reviewed.

The cresols, like the phenols which are aromatic alcohols, are topical anesthetics in low concentrations (Ref. 3). It would be expected that analgesic, anesthetic, and antipruritic effects can occur with camphorated metacresol, but there are not controlled studies to substantiate such a finding. Conclusions drawn from data obtained from the use of electrical stimulation indicate that camphorated metacresol possesses pain-reducing properties. These data are inadequate and insufficient for the Panel to make a judgment (Ref. 1). The germicidal activity of the cresols averages three or more times that of phenol (Ref. 1). The Panel has not considered the antimicrobial claims for this ingredient. Based on the insufficiency of data, the Panel concludes that camphorated metacresol must be classified as Category III as a topical analgesic, anesthetic, or antipruritic for OTC use.

(3) *Proposed dosage—For adult and children 2 years of age and older:* Apply a 0.1 to 3.0 percent concentration of camphor with metacresol, at a ratio of 66 percent camphor to 22 percent metacresol, to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 060152.

(2) Osol, a. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 400–401, 1955.

(3) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(c) *Chlorobutanol.* The Panel concludes that chlorobutanol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Chlorobutanol is 1,1,1-trichloro-2-methyl-2-propanol. It is a halogenated tertiary alcohol also known as acetone-chloroform, chloretone, chlorbutyl, methaform, acetiform, and chlorobutasol. Chlorobutanol is made by condensing acetone with chloroform in the presence of an alkali. The hydrogen atom from chloroform shifts to the ketonic oxygen atom of acetone to form a hydroxyl group and the tri-chlorinated carbon residue becomes attached to the middle carbon of the acetone molecule.

Chlorobutanol is a crystalline substance existing in two forms. One is the anhydrous form. The other is a hemihydrate. In the hemihydrate, two molecules of chlorobutanol share one molecule of water. Both the hemihydrate and the anhydrous form have a camphor-like odor and taste. Both forms of chlorobutanol sublime readily. The anhydrous form melts at 97° C. The hemihydrate form melts at 78° C. Both forms are easily soluble in water and very soluble in alcohol. One g of the anhydrous form dissolves in 1 mL alcohol and 10 mL glycerol. It is also soluble in chloroform, ether, acetone, glacial acetic acid, and various oils. The anhydrous form dissolves in liquid petrolatum to form a clear liquid solution. The hemihydrate does not form a clear solution. Chlorobutanol produces a soft mass when it is triturated with menthol, phenol, antipyrine, and certain other substances. Alkali causes chlorobutanol to break down to carbon dioxide, acetone, and other byproducts. Chlorobutanol condenses with chloral hydrate to form a stable compound that is a distinct chemical entity.

(1) *Safety.* Clinical use has confirmed that chlorobutanol is safe in the dosage range used as an OTC external analgesic.

Chlorobutanol possesses a low degree of systemic and local toxicity. Toxic doses ingested orally cause unconsciousness, coma, and death due to respiratory failure. Its systemic toxicity resembles that of chloral hydrate. Continued oral use of chlorobutanol induces tolerance. Chronic toxicity has not been demonstrated. Chlorobutanol is an old drug, having first been used systemically in 1894 by Abel as a hyponotic and as an antispasmodic of smooth muscle. Chlorobutanol is not irritating to the skin and is safe for topical application. Sensitization can occur but is uncommon (Refs. 1, 2, and 3).

(2) *Effectiveness.* Chlorobutanol is a hydroxy type of compound and has weak topical anesthetic properties on the mucous membranes. Its effectiveness topically on the skin has not been demonstrated by controlled studies. Chlorobutanol has been used systemically as a hypnotic and as an antispasmodic but possesses no analgesic effect. The hypnotic action is similar to that of chloral hydrate. It was once used for the treatment of nausea and vomiting. Presumably, it afforded relief because it acted as a topical anesthetic on the mucous membranes of the stomach and at the same time produced sedation after absorption. Its value for this purpose has been questioned and it is doubtful that it was effective as claimed because data to

support these contentions are not available. It has also been used in the treatment of coughs, hiccups, and other spasmodic conditions.

Chlorobutanol was formerly incorporated with talc as a dusting powder for the treatment of pruritus and other dermatologic conditions. It has been incorporated in suppositories for the treatment of painful hemorrhoids. However, it is no longer used for these purposes. A 1-percent solution of chlorobutanol in petrolatum has been used for the treatment of otitis media. A 25-percent solution in clove oil has been used as a dental analgesic for the treatment of toothache. It has been added to vasoconstrictors in nasal sprays to anesthetize the mucous membranes and thereby prevent the burning and stinging sensation of the vasoconstrictor. Chlorobutanol is also used as a bacteriostatic agent in vaccines and solutions of various drugs (Refs. 3 and 4).

The Panel considered several submissions in which chlorobutanol was one of the ingredients present in a combination (Refs. 5, 6, and 7). This mixture contained chlorobutanol combined with 1.18 percent menthol, 0.5 percent benzocaine, and 3.92 percent tannic acid. The Panel does not consider the data available in either the submission or the available textbooks sufficient to classify chlorobutanol as an effective external analgesic.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 1 to 5 percent concentration of chlorobutanol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See Part III, paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III, paragraph C. below—Data Required for Evaluation.)

References

(1) Cushny, M., "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 314, 1947.

(2) Dalili, H. and J. Adriana, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itching, Burning and Pain in Normal 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(3) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 290, 1973.

(4) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthesia," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 398–473, 1962.

(5) OTC Volume 060011.

(6) OTC Volume 060025.

(7) OTC Volume 060080.

d. *Cyclomethycaine sulfate.* The Panel concludes that cyclomethycaine sulfate is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Cyclomethycaine sulfate is a topical anesthetic. Chemically, it is the cyclohexyloxybenzoic acid ester of 2-methylpiperidino propyl alcohol. It is a "caine" type of drug, having the general configuration of an aromatic nucleus, a dimethylene chain, and a tertiary amino group common to these drugs, but differing from the usual structure in that the pivot has three carbon atoms instead of two. The nitrogen atom forms a tertiary amine by virtue of its position in a methylpiperidino ring on carbon 3 of the propyl alcohol. Cyclomethycaine sulfate is an ester type of topical anesthetic. It is chemically allied to piperocaine, which is a benzoic acid ester. The compound was introduced in 1946 by McElvain and co-workers who also introduced piperocaine (Ref. 1). Cyclomethycaine is a base that forms salts with acids, such as hydrochloric or sulfuric acid. Both the hydrochloride and sulfate are available, but because no data were submitted on the hydrochloride salt, the only salt evaluated by the Panel is the sulfate. The sulfate is soluble in water and stable when exposed to air and light.

(1) *Safety.* Clinical use has confirmed that cyclomethycaine sulfate is safe in the dosage range used as an OTC external analgesic.

Cyclomethycaine sulfate is a "caine" type of drug and demonstrates a qualitatively similar toxicity systemically, as do other "caine" drugs. The LD_{50} intravenously in mice is 547 mg/kg. Subcutaneously in mice the LD_{50} is 447 mg/kg and in rats, 1,079 mg/kg.

Although cyclomethycaine is chemically allied to piperocaine, it is less toxic in mice than piperocaine. The LD_{50} intravenously for piperocaine is 32 mg/kg while the subcutaneous LD_{50} dose is 589 mg/kg. Rats injected for 4 weeks with doses ranging from 50 to 500 mg/kg showed no evidence of chronic toxicity.

The lethal dose for man is not known. A transitory stinging or burning is sometimes experienced before the onset of anesthesia. Sensitization is uncommon. Its sensitizing potential is no greater than that of other "caine" type drugs. Tenely and Friedman (Ref. 2) reported one case of a 2-month-old infant who developed convulsions, congestive heart failure, and heart block after application of cyclomethycaine combined with methapyrilene to extensive surfaces of the body for seborrheic dermatitis. The surface was abraded. The symptoms receded after the preparation was washed off and supportive measures instituted. The cardiac depression and convulsions suggest that the reaction was due to the cyclomethycaine. Blood levels were not determined.

A case of anaphylactoid reaction following the use of a rectal suppository in a patient has been reported (Ref. 3). Skin reactions due to irritation or sensitization may occur in hypersensitive individuals. Marketing experience shows 4 cases of minor adverse reactions in 1,500,000 units sold.

(2) *Effectiveness.* Cyclomethycaine sulfate is a potent topical anesthetic with a rapid onset of action that may persist for several hours. Cyclomethycaine is effective as a topical anesthetic on the cornea of rabbits in concentrations as low as 0.05 percent. The duration of anesthesia is approximately 12 minutes. Concentrations of 0.5 to 1 percent increased the duration to 60 minutes. Evidence of irritation appears when concentrations exceeding 0.05 percent are used. In man, concentrations of 0.05 percent produced doubtful results. It is effective in intracutaneous wheals on guinea pigs and man. In early studies after the introduction of cyclomethycaine, 429 patients with burns, lacerations, abrasions, and other minor skin lesions were treated with cyclomethycaine preparations with satisfactory results. These studies were not controlled (Ref. 3).

Cyclomethycaine sulfate does not appear to retard healing of minor superficial cutaneous lesions. It is indicated for the relief of burning, itching, or pain associated with damaged or diseased skin and mucous membranes of the rectum and the genitourinary tract. It is not effective on the mucosa of the mouth, nose, trachea, bronchi, and the eye. It is used for the temporary relief of discomfort due to burns, superficial cuts, itching, and insect bites. As is the case with other topical anesthetics of this type, the salt does not readily penetrate intact skin.

Adriani and Dalili found that it was not effective on intact skin burned by ultraviolet light (Ref. 4).

Brockemeyer and Guth noted in preliminary tests that ointments containing 1 percent cyclomethycaine sulfate produced only slight local anesthesia. They further noted that ointments containing 5 percent cyclomethycaine sulfate produced a "marked degree" of local anesthesia (Ref. 5).

Cyclomethycaine sulfate has been used in the concentrations specified in the proposed dosage section below, but the Panel concludes that there are insufficient clinical data and a lack of sufficient controlled studies of the ingredient as a topical analgesic and anesthetic to support the effectivenss of such concentrations.

(3) *Proposed dosage—For adults and children 2 years of age or older:* Apply a 0.5 to 1.0 percent concentration of cylcomethycaine sulfate to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning.* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) McElvain, S. M., and T. P. Carney, "Piperidine Derivatives. XVII. Local Anesthetics Derived from Substituted Piperidinoalcohols," *Journal of the American Chemical Society*, 68:2592–2600, 1946.

(2) Tenley, J. A. and S. Friedman, "A Toxic Cardiac Reaction to Drugs Absorbed Percutaneously," *Pediatric Pharmacology and Therapeutics*, 69:299–301, 1966.

(3) OTC Volume 060141.

(4) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia*, 50:834–841, 1971.

(5) Brockemeyer, E. W. and E. P. Guth, "A Measurement of the Efficiency of Ointment Bases in Releasing a Local Anesthetic," *Journal of the American Pharmaceutical Association*, 44:706–709, 1955.

e. *Eucalyptus oil.* The Panel concludes that eucalyptus oil is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical counterirritants.

Eucalyptus oil is also known as oil eucalyptus and oil of eucalyptus. Eucalyptus oil is a volatile oil prepared by steam distillation from leaves of *Eucalyptus globulus* and other species of *Eucalyptus myrtaceae* containing 70 to 80 percent eucalyptol (Ref. 1). Eucalyptus oil is a colorless to pale yellow volatile liquid with a camphoraceous odor and cooling taste (Ref. 2). The eucalyptus tree is native to Australia, Tasmania, and Malaysian regions. The characteristic odor of eucalyptus oil is considered a "medicinal" odor by the laity.

One of the chief constituents of eucalyptus oil is eucalyptol, also known as cineol, cineole, cajeputol, and cajuptol. Eucalyptol is a colorless liquid with a characteristic aromatic camphoraceous odor. It is insoluble in water and miscible with alcohol, chloroform, and ether. Eucalyptus oil and eucalyptol have both been categorized in the National Formulary as flavors. They have both been categorized as having a mildly topical anesthetic, analgesic, and antiseptic effect. They have also been used as stimulating expectorants and as vermifuges (Ref. 3).

Eucalyptus oil has been used topically for the treatment of certain forms of skin disease. It is an active germicide, but not as effective as many other volatile oils (Ref. 2).

(1) *Safety.* Clinical use has confirmed that eucalyptus oil is safe in the dosage range used as an OTC external analgesic.

Eucalyptus oil is recognized in "National Formulary XIII" as a flavor. It has also been used internally as a stimulating expectorant (Refs. 4 and 5).

Meyer et al. studied the percutaneous absorption of essential oils. They found eucalyptol to be a substance showing fairly active topical absorption (Ref. 6). If eucalyptus is taken internally in large quantities as the oil or as the active ingredient eucalyptol, toxic symptoms may occur. These symptoms include epigastric burning, nausia, vomiting, tachycardia, dizziness, muscular weakness, a feeling of suffication, and in severe cases, delirium and convulsions. Death has occurred in about one-third of the human subjects who ingested between 10 and 30 mL of the oil. Idiosyncrasy toward small doses my be manifested by skin eruptions (Refs. 7 and 8). Sensitization to eucalyptus oil has been observed but is believed to occur infrequently (Refs. 9 and 10).

A study by Jenner et al. found that the LD_{50} for rats is 258 mg/kg, relatively safe when used topically (Ref. 11). Jori and Briatico studied the effect of giving eucalyptol subcutaneously to pregnant rats. It was found that eucalyptol greatly increased the liver microsomal activity during and after pregnancy. It was also found that this increased activity was higher in the fetal and newborn offspring (Ref. 12).

The question of carcinogenic activity of eucalyptus oil has been raised by several investigators (Refs. 13 and 14). It was found that in mice eucalyptus oil applied to the skin caused development of tumors in about 10 percent of the animals treated.

Marketing experience of a topical analgesic product containing small amounts of eucalyptus oil produced no evidence of a lack of safety (Refs. 15 and 16).

(2) *Effectiveness.* Martindale (Ref. 8), in reference to all essential oils, states that they have an irritant and rubefacient action and cause a sensation of warmth and smarting followed by mild topical anesthesia.

The Panel finds no sound scientific or sound theoretical basis for the classification of eucalyptus oil as a topical counterirritant in the dosage range deemed to be safe.

A counterirritant drug must evoke positive, perceptable irritation for a reasonable period of time following its application to healthy intact skin at a specified concentration.

The Panel finds nothing in the literature or in the submissions to the Panel to support a conclusion that eucalyptus oil or eucalytol has a unique vehicle-related irritancy, or that eucalyptus oil contributes any irritant activity to the formulation(s) in which it is employed.

Although eucalyptus oil has been used in concentrations ranging from 0.5 to 3.0 percent, there is insufficient data to support the effectiveness of such concentrations.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 0.5 to 3.0 percent concentration of eucalyptus oil to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical counterirritant active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See

part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 510, 1976.

(2) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, pp. 458–460, 1950.

(3) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 561–562, 1955.

(4) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 517, 1973.

(5) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1230, 1975.

(6) Meyer, F. and E. Meyer, "Percutaneous Absorption of Essential Oils and Their Constituents," *Arzneimittel Forschung,* 9:516–519, 1959.

(7) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 169, 1957.

(8) Todd, R. G., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 169, 1975.

(9) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 379, 1973.

(10) Sanitz, M. H. and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *Cutis,* 5:180–184, 1969.

(11) Jenner, P. M., E. C. Hagan, J. M. Taylor, E. L. Cook, and O. G. Fitzhugh, "Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity," *Food and Cosmetics Toxicology,* 2:327–343, 1964.

(12) Jori, A. and G. Briatico, "Effects of Eucalyptol on Microsomal Enzyme Activity of Foetal and Newborn Rats," *Biochemical Pharmacology,* 22:543–544, 1973.

(13) Roe, F. I. C. and W. H. Field, "Chronic Toxicity of Essential Oils and Certain Other Products of Natural Origin," *Food and Cosmetics Toxicology,* 3:311–324, 1965.

(14) Homburger, F. and E. Boger, "The Carcenogenicity of Essential Oils, Flavors, and Spices: A Review," *Cancer Research,* 28:2372–2374, 1968.

(15) OTC Volume 060013.

(16) OTC Volume 060014.

f. *Eugenol.* The Panel concludes that eugenol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Eugenol is 4-allyl-2-methoxyphenol. It is, therefore, a phenolic type of compound and belongs to the class of the hydroxy type of topical anesthetics. Eugenol is the main constituent in clove oil. It is also present in pimento, cinnamon leaves, sassafras, and canella. It is prepared synthetically from vanillin. An isomer, isoeugenol, is also known. This is found in clove, nutmeg, and ylang-ylang (Ref. 1).

Eugenol is a colorless, pale yellow liquid. It has a strong aromatic odor of clove and a pungent spicy taste. It is slightly soluble in water and miscible in alcohol, ether, chloroform, and fixed oils. The specific gravity is 1.06 to 1.07 (Refs. 2 and 3). Eugenol darkens and thickens on exposure to air. Eugenol is acid in reason and reacts with sodium hydroxide to form a salt, sodium eugenolate, which is soluble in alkaline solution. Eugenol is optically inactive (Ref. 1).

(1) *Safety.* Clinical use has confirmed that eugenol is safe in the dosage range used as an OTC external analgesic.

Eugenol is not irritating and is safe for topical application to the intact and damaged skin (Refs. 1, 4, 5, and 6). There is no known reported toxicity when eugenol is ingested orally.

Eugenol has been used internally as an antispasmodic and carminative, and is sometimes used in the treatment of flatulent colic. It is employed in dentistry as a flavoring agent and mild rubefacient in dentifrices, and also as an obtundent for hypersensitive dentine, caries, or exposed pulp. When eugenol is mixed with zinc oxide, it is used as a temporary anodyne filling (Ref. 7).

The acceptable daily intake for man is up to 5 mg/kg of body weight. Applied externally, it is used as an analgesic (Ref. 7). It is as potent an antiseptic as phenol, possessing decidely less irritant properties (Ref. 8).

The acute toxicity (LD_{50}) was found to be 2.7 g/kg in rats, and 3.0 g/kg in mice (Ref. 9). Poisoned rats have exhibited paresis of the hind legs and jaw with eventual prostration and coma. Death is believed to be due to peripheral vascular collapse, with surviving rats showing hematuria (Ref. 9). Eugenol is not corrosive, like phenol, but ingestion results in gastroenteritis. Systemic toxicity is less than, but similar to, phenol. Aqueous emulsions taken by mouth induce vomiting in man and dogs and promote gastric secretion of mucus (Ref. 9).

A 5-percent eugenol emulsion stimulates secretion of gastric mucus without an increase of acid. Three or four applications of eugenol at 3-hour intervals to the gastric mucosa exhausts the mucous response after which a nonviscous exudate is released. Partial recovery occurs in 30 hours, but complete recovery usually requires 3 to 5 months (Ref. 10).

(2) *Effectiveness.* Eugenol has been used in dentistry for disinfecting root canals, as a topical analgesic for the relief of hypersensitive dentine pain and irritation due to hyperemic inflamed viral polyps, and as a component of a zinc eugenol cement used as a temporary filling for carious teeth (Refs. 1, 4, and 5). Formerly, eugenol was used internally as an antiseptic and as an antiputrescent, but it is no longer employed for this purpose. Eugenol appears to be slightly less active as an antiseptic than the natural oil. Eugenol stimulates peristalsis by virtue of its local irritant effect and has been used in the treatment of flatulent colic (Ref. 1). It also possesses some topical anesthetic action by virtue of its phenolic nature, being a favored remedy for toothache. Small pledgets of cotton saturated with the oil are inserted into the carious cavity. However, its topical anesthetic action is considered to be weak and evanescent. Eugenol manifests antimicrobial activity in some cases, being approximately eight times stronger than phenol in this respect. But because of its irritant properties on the mucous membranes, it is not frequently used for this purpose except by dentists. The Panel did not receive data in any submission, and was unable to find data in controlled or uncontrolled studies, to substantiate the claims that eugenol is a topical analgesic, anesthetic, and antipruritic (Ref. 11). Although 1 to 2 percent concentrations of eugenol have been used clinically, there is insufficient evidence as to the effectiveness of such preparations.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 1 to 2 percent concentration of eugenol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. Below—Data Required for Evaluation.)

References

(1) Osol, A., "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 565, 1955.

(2) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 193, 1975.

(3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 551, 1976.

(4) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 1036, 1971.

(5) Grollman, A. and E. F. Grollman, "Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, p. 416, 1970.
(6) Stecher, P. G., "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 440, 1960.
(7) Todd, R. G., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, pp. 1239–1241, 1972.
(8) Dobbs, E. C., "Pharmacology and Oral Therapeutics," C. V. Mosby Co., St. Louis, p. 448, 1961.
(9) Gosselin, R. E., H. C. Hodge, R. P. Smith, and M. N. Gleason, "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 168, 1975.
(10) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 170, 1957.
(11) OTC Volume 060007.

g. *Glycol salicylate.* The Panel concludes that glycol salicylate is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Glycol salicylate is also known as glycol monosalicylate, monoglycol salicylate, ethylene glycol monosalicylate, and 2-hydroxyethyl salicylate. It is the mono ester of ethylene glycol. It is prepared synthetically by esterification of ethylene glycol with salicylic acid. Its chemical nature and pharmacologic activities appear to be similar to methyl salicylate. It is a colorless, odorless liquid that boils at 169° to 172° C. One part of glycol salicylate is soluble in 110 parts water and in 8 parts olive oil. It is very soluble in alcohol, benzene, chloroform, and ether (Ref. 1).

(1) *Safety.* Clinical use has confirmed that glycol salicylate is safe in the dosage range used as an OTC external analgesic. In full strength concentrations, it has an irritant effect on the skin. Toxicity from oral ingestion is alleged to be due to the release of salicylate in the bowel and the absorption of the salicylate into the bloodstream. The symptoms are similar to those induced by other esters of salicylic acid.

Glycol salicylate is an ester of ethylene glycol. Absorption of the drug through the skin or after oral ingestion may result in hydrolysis of the ester to ethylene glycol and salicylic acid. Ethylene glycol is oxidized to oxalic acid in the body. Oxalic acid is toxic if excessive quantities form. The Panel has no proof that this occurs with this ingredient when applied topically but feels this should be a point of interest in considering safety.

(2) *Effectiveness.* Glycol salicylate possesses no significant topical anesthetic activity and does not block the neuronal membranes as do the topical anesthetics, such as benzocaine, butamben, etc. It lacks sufficient counterirritant activity to be classified as a counterirritant. Although some degree of percutaneous absorption of salicylate esters occurs through the intact skin, no significant topical analgesic or anesthetic activity can be demonstrated. The Panel has insufficient evidence to classify glycol salicylate as a counterirritant.

It is claimed that glycol salicylate exerts its effect topically to relieve pain in muscles and structures beneath the skin by acting as an anti-inflammatory agent, as do other salicylates. Glycol salicylate does not act as a counterirritant in the dosage form described below. Salicylate blood levels have been demonstrated after topical application in animals, but these have not been correlated with those occurring after oral ingestion of salicylate analgesics. Excretion of salicylates or metabolites has been demonstrated in the urine, but this is not proof of effectiveness. Claims are made that localized areas of myalgia and other painful musculo-skeletal disorders are relieved by the application of esters of salicylic acid to the affected part. The Panel concludes from available data that this action, if indeed analgesia results, is due to a systemic effect, and any analgesic effect is due to the blood-borne drug.

No evidence that relief of pain is due to a counterirritating effect of the drug has been submitted from controlled studies. It is employed at concentrations of 1.9, 1.93, and 10 percent in combination products. In these combinations, counterirritants are included in the formulation. Data from controlled studies demonstrating the analgesic effect claimed has not been available.

The exact mechanism by which salicylates produce their analgesic effects is not known, but it is generally conceded that they act in part centrally, and in part by exerting an anti-inflammatory effect peripherally, as does aspirin, by inhibiting prostaglandin synthesis. (See part III. paragraph B.3.a. above—Aspirin.) It is possible that the salicylate activity of glycol salicylate may also be due to an inhibitory effect on prostaglandin synthesis. There is no evidence that cutaneous analgesia or anesthesia results.

The Panel does not give serious consideration to the claim that glycol salicylate penetrates the skin and passes directly into the affected deeper structures to exert its analgesic effect. Although 8 to 10 percent concentrations of glycol monosalicylate have been used clinically, there is insufficient evidence on the effectiveness of such concentrations.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply an 8 to 10 percent concentration of glycol salicylate to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1 above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 583, 1976.

h. *Hexylresorcinol.* The Panel concludes that hexylresorcinol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Hexylresorcinol, an aromatic alcohol, is a dihydroxybenzene with a normal hexyl group on position 4 and hydroxyl groups on positions 1 and 3 of the aromatic nucleus. It is, therefore, classifiable as a phenol. It responds to certain specific chemical tests characteristic of phenols. Hexylresorcinol is prepared by condensing resorcinol with caproic acid in the presence of zinc chloride. The resulting intermediate product is reduced to hexylresorcinol (Refs. 1, 2, and 3).

Hexylresorcinol is a white or yellowish-white powder composed of needle-shaped crystals. It has a faint "fatty" odor and a sharp astringent taste. When placed on the tongue, the ingredient produces a sensation of numbness. Hexylresorcinol melts at between 62° and 67° C. It turns from a white to a brownish-pink tint on exposure to light and air due to oxidation to quinones. One g of hexylresorcinol dissolves in

approximately 2,000 mL of water. It is freely soluble in alcohol, methanol, glycerine, ether, chloroform, benzene, and vegetable oils. For many years hexylresorcinol was considered official and was included in the "United States Pharmacopeia."

(1) *Safety.* Clincial use has confirmed that hexylresorcinol is safe in the dosage range used as an OTC external analgesic.

Because hexylresorcinol was extensively used as an anthelmintic and adminstered orally in both adults and children, the Panel considers it to be safe for topical application to the skin (Ref. 4). The usual adult dose as an anthelmintic is 1 g as a single dose in a 24-hour period. For children, the usual dose is 0.1 g for each year of age up to 10 years. The drug is usually given orally after an overnight fast. The presence of food lessens the effectiveness of the drug. A saline purge is usually given the following morning to clear the bowel of dead worms. Treatment may be repeated after 3 days (Ref. 1). Hexylresorcinol has also been shown to have some antimicrobial effects. The drug has been used as a gargle and as a urinary antiseptic. Experiments by Leonard (Ref. 5) resulted in the use of hexylresorcinol as a urinary antiseptic. He found that hexylresorcinol at pH 6 to 6.4 in a 1:60,000 concentration killed microbes in the urine in 1 hour, and that at pH 7.6 to 8.2, a concentration of 1:18,000 was required for the same effect. Robbins (Ref. 6) observed that after oral administration of hexylresorcinol to man, 18 percent was eliminated in the urine in a conjugated form, and 64 percent was eliminated in the feces in an uncombined state.

Animal studies indicate a low degree of acute and chronic toxicity. In rats, the oral minimum lethal dose of a suspension is 50 mg/kg. A suspension in 5 percent olive oil solution administered subcutaneously resulted in a minimum lethal dose of 750 to 1,000 mg/kg. A similar low degree of toxicity was found in guinea pigs, rabbits, cats, and dogs. In dogs, doses of 1 to 3 g produced no signs of toxicity. When the dogs were sacrificed, mild irritation of the stomach was noted 4 to 5 hours after ingestion of the drug. Lesions in the mucosa were superficial. If the animals were sacrificed 48 hours later, the lesions were not present. Oral administration in rats revealed no signs of toxicity when a dose of 12 mg/kg was given 6 times over an 8-hour period and was well tolerated (Ref. 7).

Pure hexylresorcinol is irritating to the respiratory tract and to the skin. A concentrated solution of hexylresorcinol in alcohol has vesicant properties. It lacks the irritancy and caustic properties of resorcinol and phenol. Use over a period of 40 years and extensive marketing experience indicate that hexylresorcinol possesses a low degree of sensitization.

(2) *Effectiveness.* The Panel finds that hexylresorcinol has been used as an analgesic, anesthetic, and antipruritic on the skin to relieve pain due to sunburn. In one study (Ref. 7) 100 adults participated. Their ages ranged from 14 to 74 years. Fifty subjects were treated with another agent. All 50 subjects treated with 0.1 percent hexylresorcinol obtained relief from pain and discomfort due to sunburn. No other clinical studies are available for the use of hexylresorcinol on the skin. However, hexylresorcinol is a phenol, and the substitution of an aliphatic radical on the side chain of this phenol attenuates the caustic activity but allows the retention of its phenolic qualities, which include analgesic, anesthetic, and antipruritic activity. Therefore, it is the Panel's opinion that hexylresorcinol does have analgesic properties.

In the cornea of rabbits, hexylresorcinol solution, 0.1 percent, produces topical anesthesia lasting various periods of time up to 10 minutes or more depending on the concentration of the hexylresorcinol. Hexylresorcinol has been incorporated in lozenges for the relief of sore throat and other painful ailments of the oral cavity.

Adriani and DiLeo (Ref. 8) found that the application of a commercial preparation consisting of a 1:1000 solution produced analgesia on the gums and at the tip of the tongue, after stimulation by an electric current, but did not completely abolish sensation. With the exception of this study, the Panel has not received other reports of controlled studies on the analgesic effect of hexylresorcinol on the intact or damaged skin.

The ingredient has been recommended as an antimicrobial agent for cuts, wounds, and burns, but judgment of its effectiveness for these conditions does not come under this Panel's purview.

The range between the minimum effective dosage and the maximum allowable dosage as an external analgesic on the skin has not been established with certainty. The Panel questions the dosage recommended in the labeling of products on the market, which is that the ingredient be used full strength (0.1 percent) or diluted with an equal part of water. Therefore the Panel recommends that the effectiveness of this dosage range be adequately tested. (See part III. paragraph C. below—Data Required for Evaluation.)

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 0.05 to 0.1 percent concentration of hexylresorcinol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 582–583, 1973.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 618, 1976.

(3) Osol, A. and G. E. Farrar, "The Dispensatory of the United States," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1691–1692, 1955.

(4) Brown, E. A., W. Krabek, and R. Skiffington, "A New Antiseptic Solution for Topical Application (Comparative In Vitro Studies)," *New England Journal of Medicine,* 234:468–472, 1946.

(5) Leonard, V., "Secretion of Bactericidal Urine and Disinfection of Urinary Tract Following Oral Administration of Certain Alkyl Derivatives and Resorcinol," *Journal of the American Medical Association,* 83:2005–2012, 1924.

(6) Robbins, B. H., "Quantitative Studies on the Absorption and Excretion of Certain Resorcinols and Cresols in Dogs and Man," *Journal of Pharmacology,* 52:54–60, 1934.

(7) OTC Volume 060138.

(8) Adriani, J. and J. DiLeo, "The Effectiveness of Hexylresorcinol as a Topical Analgesic on the Mucous Membranes of the Oral Cavity," Draft of unpublished paper, in OTC Volume 060150.

i. *Salicylamide.* The Panel concludes that salicylamide is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Salicylamide, the amide of salicylic acid, is 2-hydroxybenzamide. It is a white, crystalline, almost odorless powder. It is poorly soluble in water. One g dissolves in 500 mL water, 15 mL alcohol, 100 mL chloroform, and approximately 35 mL ether (Refs. 1 and 2).

(1) *Safety.* Clinical use has confirmed that salicylamide is safe in the dosage range used as an OTC external analgesic.

Although salicylamide is the amide of salicylic acid and is generally discussed along with the salicylates as an analgesic, it is not converted to free salicylates in the body when the ingredient is ingested orally (Ref. 1). It is rapidly conjugated with glucuronic and sulfuric acids by enzymes in the mucosal wall of the intestines and the liver. The conjugates are excreted into the urine. Patients sensitive to aspirin apparently are not sensitive to salicylamide, because it is not converted to salicylic acid or any of its salts or esters. Its use topically is safe and it causes no irritation to the skin (Ref. 3).

Spickard (Ref. 3) reported no evidence of irritancy after application of a preparation containing 5 percent salicylamide and 1 percent benzocaine dissolved in isopropyl alcohol and polyoxyethylene lauryl ether to 237 subjects. Three drops were applied to the forearm every other day. Readings for any evidence of rash or irritation were made 24 hours after each application. After a series of 10 applications and a rest period of 10 days, a single repeat application was made and the effects of this application were noted 24 hours later. Seven subjects reacted with itching and redness after the first or subsequent applications. After the 10-day rest period, only two individuals reacted. The two individuals would be considered to have shown an allergic reaction according to the Draize method.

Salicylamide is used orally as an analgesic; however, there is some question concerning its safety after oral ingestion. The oral lethal dose of salicylamide in man has not been established. A minimum of 1,000 mg administered orally every 4 hours must be used to obtain analgesia, but not more than 6,000 mg should be used in 24 hours. This dosage must not be used for more than 10 days (see the report of tthe Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products, published in the **Federal Register** of July 8, 1977 (42 FR 35346)). Higher oral doses of salicylamide may produce drowsiness, dizziness, and gastrointestinal upset (Ref. 1). Another toxic manifestation in analgesic dosages is hepatic insufficiency in children. Damage to blood-forming elements following chronic use is sufficiently serious to warrant additional study. Whether sufficient quantities are absorbed through the skin to produce these effects is not known, but none of these adverse reactions has been brought to the attention of the Panel. Salicylamide, in contrast to aspirin and other salicylates, has no effect on the clotting mechanism or platelet aggregation and does not affect bleeding time or clotting time. Allergic reactions to salicylamide are rare. Cross-sensitivity to aspirin does not occur.

(2) *Effectiveness.* Salicylamide or its metabolites can be detected in the urine when the drug is applied topically to the skin (Ref. 3). A submission to the Panel contained the following statement: "The determination of blood levels in rabbits and of the urinary excretion in humans and in rabbits of benzocaine and salicylamide had established that the active ingredients are absorbed through the intact skin. However, these experiments did not permit any direct conclusion concerning the possible penetration of these drugs into the muscle tissues." The Panel agrees with these statements in the submission. The following statement is also found in the submission: "By inference, such a penetration is indicated by the relief of pain following topical application." The Panel does not agree with this statement, however (Ref. 3).

Studies carried out in six rats revealed the presence of salicylamide in muscle tissue. The Panel does not disagree that percutaneously absorbed drugs can be detected in tissue, because such drugs pass into the systemic circulation and are redistributed to various organs and tissues. However, the mere presence of the drugs in tissues does not necessarily mean that their effect is based there, unless the tissue concentration approaches that found in the plasma when these drugs are given orally and cause their effects. No data derived from controlled studies in man have been submitted to substantiate claims of pain relef in muscles and other structures beneath the skin. Evidence of pain relief in a double-blind, crossover type of study would be helpful in making a judgment.

Letters from users of the marketed preparation describing the relief of muscular aches and pains were submitted as evidence of muscular aches and pains were submitted as evidence of the effects claimed in the labeling (Ref. 3). The Panel regards these reports as anecdotal and considers them to be testimonials not based on facts. Factual data to substantiate the claims made in the labeling have not been submitted.

When ingested orally, salicylamide is almost completely metabolized to pharmacologically inactive substances during its passage from the gastrointestinal tract to the liver, before it is even absorbed into the systemic circulation to become available at the therapeutic site of action. This initial absorption before it becomes therapeutically effective in sufficient concentrations in the systemic circulation is sometimes referred to as the absorptive phase. In this absorptive phase, the salicylamide is metabolized by conjugation with glucuronic acid and sulfuric acid. The conjugates are excreted into the urine. The biotransformation at low oral doses is so extensive that little, if any, active unmetabolized drug is available for absorption into the systemic circulation for distribution to the sites of therapeutic action (see 42 FR 35346, July 8, 1977) (Ref. 4).

Because the drug is poorly water soluble, the Panel feels the amount available for absorption via the skin is limited. The bioavailability through the skin, therefore, is questionable. Evaluations of analgesic potency of salicylamide in animals indicate that a wide range of effectiveness exists and that there is considerable disparity between the results of different observers when the drug is compared to aspirin. In man, however, salicylamide has been shown to have little, if any, superiority over aspirin. Oral doses below 600 mg are not effective and the analgesic effects are indistinguishable from the placebo. For two reasons the Panel doubts that quantities absorbed through the skin are effective, even when blood-borne. First, the substance is metabolized quickly, and second, its efficacy is questionable because the effect of 600 mg orally is indistinguishable from placebo. It is doubtful that 600 mg is absorbed by local application to the skin. Furthermore, salicylamide has no anti-inflammatory activity (see 42 FR 35346, July 8, 1977).

The Panel has had no evidence submitted to it that salicylamide possesses topical anesthetic activity and blocks neuronal membranes as do the topical anesthetics of the "caine" type, such as benzocaine, tetracaine, lidocaine, etc. There is no evidence that salicylamide possesses topical analgesic, anesthetic, or antipruritic activity for the relief of cutaneous disorders (Ref. 3).

There is no disagreement that some degree of percutaneous absorption of salicylic acid derivatives occurs through the intact skin (Ref. 5). Blood levels of salicylates have been demonstrated in animals. Claims are made that pain and discomfort resulting from myalgia and other musculoskeletal disorders are relieved by the application of

preparations containing derivatives whose effect is systemic and that any analgesic effect is due to the blood-borne drug. The Panel does not consider the quantity that would be absorbed by percutaneous routes to be sufficient to induce analgesia systemically as is the case with oral preparations. The exact mechanism by which derivatives of salicyclic acid produce their analgesic action is not known, but it is generally conceded that they act not only centrally but also in part by exerting an anti-inflammatory effect. Not all derivatives of salicylic acid exert anti-inflammatory effects. Salicylamide does not have an anti-inflammatory effect. Therefore the Panel does not give serious consideration to the claim that the drug penetrates the skin and passes directly into the affected deeper structures to exert an analgesic effect (see 42 FR 35346, July 8, 1977).

Salicylamide has been used in a concentration of 35 percent with benzocaine.

(3) *Proposed dosage—For adult and children 2 years of age and older:* Apply a 3 to 10 percent concentration of salicylamide to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1033, 1973.

(2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1079, 1976.

(3) OTC Volume 060119.

(4) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, p. 348, 1975.

(5) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co. Philadelphia, p. 1035, 1973.

j. *Thymol.* The Panel concludes that thymol is safe but there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Thymol, also known as thyme camphor, is 5-methyl-2-isopropyl-1-phenol. It may be prepared synthetically or obtained from volatile oils distilled from *Thymus volgaris* and other related plant sources. Thymol occurs as colorless crystals, which are often large, or as a white crystalline powder. It melts at 51° C and boils at 233° C. One g dissolves in 1 liter water. It is highly soluble in alcohol, chloroform, and in mineral oil and other fixed and volatile oils (Ref. 1). It has a characteristic aromatic thyme-like odor and a pungent taste. Thymol has appreciable volatility in water vapor when it is prepared in aqueous solutions.

(1) *Safety.* Clinical use has confirmed that thymol is safe in the dosage range used as an OTC external analgesic.

Thymol has a pleasant aromatic odor. In the past, it has found its way into a wide variety of medicinal uses but has in many cases been superseded by other newer and more effective drugs. It has been incorporated into mouthwashes for its antiseptic action and has been used topically and orally for the treatment of actinomycosis. It has also been used internally as an intestinal antiseptic and anthelmintic, especially against hookworm (Refs. 2 and 3).

The LD_{50} in mice was found to be 74 mg/kg when thymol was injected intravenously (Ref. 4). Jenner (Ref. 5) studied the acute oral toxicity of thymol by intubation in the rat and guinea pig. The LD_{50} for the rat was found to be 980 mg/kg, and for the guinea pig, 880 mg/kg.

Chronic toxicity was observed in five male and four female rats given an oral dose of 10,000 parts per million for 19 weeks. No untoward effects were found (Ref. 6).

Ingestion of 1 g thymol usually does not cause any adverse symptoms other than a feeling of warmth generated in the stomach. Doses larger than 1 g have resulted in gastrointestinal irritation marked by dizziness, excitement, and severe epigastric pain, followed by vomiting, nausea, marked weakness, sweating, collapse, and slowed pulse and respiration. Abortion has also resulted (Ref. 3).

Worm infestations have been treated in the past with thymol, especially in the Far East. A report by Barnes noted that over a million doses of thymol averaging 1 g per dose resulted in reported deaths of 20 debilitated patients (Ref. 7).

Samitz and Shmunes noted that dentists and other allied personnel found thymol one of the less frequent sensitizers in occupational dermatoses (Ref. 8). Thymol irritates the mucous membranes, but has little effect when applied topically to the skin and is virtually unabsorbed (Ref. 3). The oral toxicity of thymol is about one-fourth that of phenol; if absorbed, half is metabolized totally, and the remainder is conjugated with sulfuric and glucuronic acids and excreted into the urine (Ref. 3).

(2) *Effectiveness.* Thymol was first introduced as a disinfectant. It has a phenol coefficient of 27.6, but its activity is greatly reduced in the presence of proteins. It also has some antiviral activity (Ref. 9). Potter, in 1891 (Ref. 10), stated that thymol was a topical anesthetic for use on the skin and mucous membranes. Buckley (Ref. 11) also noted that thymol had topical analgesic properties and considered it superior to phenol as an antiseptic.

Thymol has been referred to another Panel for the determination of its safety and efficacy as an antimicrobial and antifungal agent.

The Panel concedes it is possible that thymol is a topical analgesic, anesthetic, and antipruritic because of its phenolic nature, but the Panel does not have sufficient evidence and documentation to support this claim. Most of the literature refers to the antimicrobial and antifungal effects of thymol. Although 1 to 2 percent concentrations of thymol have been used clinically for topical analgesia and anesthesia, there is insufficient evidence of the effectiveness of such concentrations.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 1 to 2 percent concentration of thymol to affected area not more than 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1189–1190, 1973.

(2) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1101, 1975.

(3) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227–228, 1957.

(4) Edwards, E. H. and B. Hall, "Thymol as a Bacteriostatic Agent," *The Pharmaceutical Journal*, 166:54, 1951.

(5) Jenner, P. M., E. C. Hagan, J. M. Taylor, E. L. Cook, and O. G. Fitzhugh, "Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity," *Food and Cosmetics Toxicology*, 2:327–343, 1964.

(6) Hagan, E. C., W. H. Hansen, O. G. Fitzhugh, P. M. Jenner, W. I. Jones, J. M. Taylor, E. L. Long, A. A. Nelson, and J. B. Brouwer, "Food Flavorings and Compounds of Related Structure. II. Subacute and Chronic Toxicity," *Food and Cosmetics Toxicology*, 5:141–157, 1967.

(7) Barnes, M. E., "Death Following the Administration of Thymol," *Journal of the American Medical Association*, 79:964–965, 1922.

(8) Samitz, M. H. And E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *Cutis*, 5:180–184, 1964.

(9) Dunham, W. B. and W. J. MacNeal, "Culture on the Chick Chorioallantosis as a Test of Inactivation of Coccinea Virus," *Journal of Bacteriology*, 44:413–424, 1942.

(10) Potter, S., "Handbook of Materia Medica Pharmacology and Therapeutics," 3d Ed., Blakiston Press, Philadelphia, p. 389, 1891.

(11) Buckley, J. P., "Modern Dental Materia Medica Pharmacology and Therapeutics," 5th Ed., W. B. Saunders Co., Philadelphia, pp. 48, 50, and 515, 1926.

k. *Triethanolamine salicylate.* The Panel concludes that triethanolamine salicylate is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC external analgesic. During the testing period provided to demonstrate effectiveness, the ingredient may bear the labeling provided for topical analgesics, anesthetics, and antipruritics.

Triethanolamine salicylate is an ester produced by the interaction of equal amounts of triethanolamine and salicylic acid. Triethanolamine salicylate is a light reddish, viscous liquid with a faint odor and a specific gravity of 1.280 to 1.980. Triethanolamine salicylate is miscible in all proportions with water, glycerine, propylene glycol, isopropyl alcohol, and 95 percent ethyl alcohol. It is insoluble in mineral oil and vegetable oils.

(1) *Safety.* Clinical use has confirmed that triethanolamine salicylate is safe in the dosage range used as an OTC external analgesic.

The oral LD_{50} of triethanolamine salicylate in rats is 2.8 g/kg. Animal and human toxicological data indicate that it is safe for topical application. Its average Draize primary skin irritation index is 1.5. Triethanolamine salicylate is not a topical irritant and has minimal sensitizing potential (Refs. 1, 2, and 3). An intracutaneous sensitization test in 10 guinea pigs over 5 weeks revealed no sensitization reactions on repetitive examinations. Repeated insult patch tests of the lotion formulation, using the Draize human skin irritancy test in 52 women and 5 men gave the following results: After 9 applications to the upper arm in 21 days and a challenge at 35 days, there was revealed a slight erythema at the application sites in 4 individuals. This is presumptive evidence that triethanolamine salicylate is not a sensitizer (Ref. 2).

(2) *Effectiveness.* Triethanolamine salicylate, which penetrates the intact and damaged skin, does not block the neuronal membranes as do the topical anesthetics, such as benzocaine, etc., and therefore possesses no topical anesthetic activity. Some degree of percutaneous absorption of salicylic esters occurs through the intact skin (Refs. 4, 5, and 6), but no significant analgesic or anesthetic activity has been demonstrated. Blood levels have been demonstrated following topical application with various techniques in animals. These blood levels have not been correlated to blood levesl fo salicylate-type analgesic ingredients administered by the oral route. Triethanolamine salicylate is not a counterirritant analgesic salicylate ester.

In the absence of such comparative data, the Panel does not give serious consideration to claims made for the effectiveness of triethanolamine salicylate as an analgesic for muscles aches and pains because it is doubtful that sufficient quantities are absorbed from the skin to be blood-borne. Gaudin (Ref. 7) noted that approximately 15 percent of a topically applied amount of triethanolamine salicylate on rabbit skin appeared in the urine as salicylic acid and that 9.46 percent sodium salicylate was found in the urine by comparison (Ref. 1). The Panel does not disagree that salicylates are absorbed from the skin, but it does not agree that this is proof of effectiveness of these drugs as analgesics on the structures beneath the skin to which they are applied. Excretion of salicylates or metabolites into the urine has been demonstrated (Ref. 1).

Claims have been made the localized areas of myalgai and other painful musculoskeletal disorders are relieved by the application of esters of salicylic acid to the affected part. The Panel concludes from available data that this action most likely is systemic and any analgesic effect is due to the blood-borne drug. The Panel does not believe that evidence has been provided to indicate that sufficient quantities are absorbed to induce analgesia. The exact mechanism by whcih salicylates produce their analgesic effect is not know, but it is generally conceded that they act in part centrally, and in part peripherally, by exerting an anti-inflammatory effect by inhibiting the synthesis of protaglandins. (See part III. paragraph B.3.a. above—Aspirin.)

Some evidence exists that salicylates inhibit the synthesis of prostaglandins and relieve pain in this manner. References cited in the submission for effectiveness of the ingredient refer to salicylates but provide no data concerning triethanolamine salicylate (Refs. 1 and 3). The only proof of efficacy is that salicylates are absorbed percutaneously (Ref. 8).

The Panel does not give serious consideration to the claim that the drug penetrates the skin and passes directly into the affected deeper structures in sufficient concentration to be effective because there is not data to substantiate this claim (Refs. 1 and 3).

Triethanolamine salicylate has been used topically in concentrations of 5 to 10 percent, but there are no data available to substantiate its effectiveness in that dosage range.

(3) *Proposed dosage—For adults and children 2 years of age and older:* Apply a 5 to 10 percent concentration of triethanolamine salicylate to affected area 3 to 4 times daily. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing topical analgesic, anesthetic, and antipruritic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for external analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 060024.

(2) OTC Volume 060091.

(3) OTC Volume 060144.

(4) Osol, A. and R. Pratt, "The Dispensatory of the United States," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1034–1035, 1973.

(5) Todd, R. G., "Martindale, The Extra Pharmacopeia," 25th., Ed., The Pharmaceutical Press, London, p. 26, 1967.

(6) Davison, C. and H. G. Mandel, "Nonnarcotic Analgesics and Antipyretics 1: Salicylates," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill Book Co., New york, p. 383, 1971.

(7) Gaudin, O., "Amine Salicylate Ointment," U.S. Patent: 2, 596, 674, May 13, 1952.

(8) Plein, J. B. and E. M. Plein, "A Comparison of In Vivo and In Vitro Tests for the Absorption, Penetration, and Diffusion of

Some Medicinals from Silicone and Petrolatum Ointment Bases," *Journal of the American Pharmaceutical Association*, 12:705–717, 1957.

Category III Labeling

The Panel concludes that there are insufficient data available at this time to permit final classification of the following claims:

Claims for relief of deep-seated pain. The Panel finds that there is insufficient evidence that external analgesic ingredients penetrate beneath the skin to relieve deep-seated pain. Claims such as "penetrates deep into the skin and relieves pain arising from deep down inside," "penetrating heat relief," and "deep strength" are unsubstantiated and require further testing. The Panel has classified such claims as Category III.

C. Data Required for Evaluation.

The Panel considers that the protocols recommended in this document for the studies required to bring Category III external analgesic ingredients into Category I reflect the present state of the sciences of pharmacology and toxicology. The protocols do not preclude the use of newer or more refined laboratory or clinical investigative methods to establish safety or effectiveness of an ingredient. Manufacturers are expected to furnish only data relevant to unanswered questions regarding the safety and efficacy of the ingredients in their product. They are not expected to furnish all the data listed in the guidelines below.

Safety studies are required if the data submitted to data have not substantiated claims that an ingredient is safe when applied externally on the intact or damaged skin. Efficacy studies are required if the data submitted to date have not substantiated the claim that an ingredient is effective.

1. *General considerations.* a. Pain is a subjective sensation in response to noxious stimuli. Lack of reactivity when noxious stimuli are applied without production of pain indicates that a state of analgesia has been induced. The appraisal of the analgesic activity of an ingredient or a combination of ingredients must be based upon their ability to relieve pain caused by a disease process or trauma. The pain experience in man consists of perception of painful stimuli, together with the psychologic modification of the response to these stimuli. Animal screening tests and methods using experimentally induced pain in normal human volunteer subjects generally do not yield consistent results nor are the results in humans similar to those obtained in studies of pain of pathologic origin (Ref. 1). The only exceptions the Panel considers applicable are pain due to burns of the skin induced by ultraviolet radiation and pain due to experimentally produced abrasions or excoriations. Skin pain is localized. Experimentally induced pain from ultraviolet light burns is generally the same type as pathologically induced sunburn pain, and pain due to abrasions in volunteers is similar to that caused accidentally by trauma to patients. Objective methods for studying pain in humans, either experimentally produced pain or pathologic pain, are not available. The efficacy of analgesic drugs, both in laboratory and clinical situations, must be appraised by accepting the subject's own reports on indices of pain experiences and the relief obtained by topical administration of external analgesics.

b. Certian general comments pertaining to the preparation of protocols in the evaluation applicable to all external analgesic ingredients considered by the Panel (analgesics, anesthetics, antipruritics, and counterirritants) are discussed below. Comments applicable only to analgesics, anesthetics, and antipruritics and those pertaining only to counterirritants are also considered below in separate discussions.

The Panel concludes it is reasonable to allow 3 years for the development and review of evidence that will permit final classification of the effectiveness of the Category III ingredients aspirin, glycol salicylate, salicylamide, triethanolamine salicylate, and thymol, and for the indication for deep-seated pain. The Panel concludes that it is reasonable to allow 2 years for the development of data for all other Category III conditions. The ingredients pose no serious problem for the consumer. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 or 3 years as specified, the ingredients shoud no longer be marketed in OTC products.

2. *Procedure for conducting studies on normal volunteer subjects and patient.* Investigational studies of a proper design should be conducted on human volunteers if reproduction of a particular skin condition is feasible (Ref. 2). Examples of experimental designs that may be appropriate include crossover, double-blind, factorial, sequential trial, single-blind trial, and therapeutic equivalency. Preference should be given to a double-blind study with controls, so that it will demonstrate the efficacy of the product. The cross-over technique should be used, if possible. When that technique is used, a period of 12 hours or more should be allowed to eliminate all of an absorbed drug from the system. If the identity of an ingredient cannot be masked when a double-blind study is performed, and if a suitable placebo is not available, control and treatment periods should be of sufficient duration to allow subjects to serve as their own control. The number of subjects used in such a study should be sufficient to permit statistical analysis of the data obtained (Ref. 2). The number tested should be sufficient to eliminate examiner bias, bias due to placebo effect, and the effects of psychological responses to pain in tested subjects. The subjects should be of both sexes and within the age groups for which use of the product is intended. The subjects should be healthy and free from any ailment and should not be receiving any oral, parenteral, or topical medication. Female subjects should not be pregnant. The study should be of sufficient duration to demonstrate efficacy. The treatments should be selected on a random basis. The number and frequency of the applications of the preparation should be the same as would be the case for clinical use. Any manifestation of local or systemic irritancy, sensitivity, or toxicity in these tests should be recorded.

When studies are performed in clinical situations, a large number of appropriate subjects with different types of pain should be studied. Differentiation of patients should be made in accordance with the type of pain, i.e., pain due to inflammation, burns, or that arising in joints, muscle, etc. The randomization procedure should be made so that variables not otherwise controlled balance out.

There should be detailed explanation of the criteria for assessment of the condition to be treated by the ingredient, of the method employed in testing, and of the validity of the method or methods used. A medical history, demographic data, and physical data including physical examination, laboratory studies, and other pertinent data should be obtained and recorded for each subject.

Studies should be performed on patients who have lesions, pain, burns, etc. Subjects who have similar kinds of conditions and are being treated with a preparation should be divided into a treated group and a "placebo" group to obtain a controlled study. Again, "before treatment" data should be obtained and recorded. The degree of relief of symptoms, the onset of action,

whether partial or complete, the duration of action, and the presence or absence of any rebound after the analgesic effect wears off should be noted. A grading or scoring technique should be used to determine degree of relief. The application of the medicament should be in accordance with the method outlined below and the indication for use on the labeling. The tests should be performed using the final product formulation.

The range between the minimum effective concentrations and the maximal allowable (safe) concentration should be supplied when lacking. This may be expressed as a percent concentration of the preparation. Consideration should be given to how the drug is absorbed or penetrates the skin, its duration of action, and its relationship to the length of time it remains on the skin. In cases where claims are made that a drug penetrates the skin and passes directly into deeper structures such as muscles and joints and causes relief of pain, such direct penetration and pain relief must be shown to occur. The mere fact that the drug is absorbed and is detectable in the blood, or is excreted into the urine in its pure form or as metabolites, will not be sufficient evidence of efficacy.

An attempt should be made to determine the possible mechanism of action or actions of the drug.

3. *Interpretation of data.* Records should be detailed and should include legends, with specific explanation of codes, doses, mode and time of application, the period of latency from the moment of application to the development of the desired therapeutic effect, the frequency of testing, and the duration of test period. Investigative methods should be described in detail so that the experiments can be repeated to verify and confirm results obtained by the investigator (Ref. 2).

Provision should be made to eliminate examiner bias in either volunteer or clinical trials. Proper interpretation and explanation of the results should be provided. Whenever possible, statistical analysis should be employed to evaluate the results. Consideration should be given to the placebo effect of a drug.

Evidence of drug effectiveness is required from a minumum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

4. *Safety evaluation.* Adequate, acceptable controlled in vivo studies of acute and chronic toxicity in several species of animals should be supplied. The oral LD_{50} in animals should be established. The range of the toxic dose in humans should be made available if possible, because individuals, especially children, may accidentally ingest or inhale overdoses of these medications (Ref. 2). If the ingredient has been classified Category III for safety reasons, studies on chronic toxicity should be performed by two independent investigators over a 3-month period.

Tests should be performed for acute eye irritancy, primary skin irritancy, corrosivity, acute dermal toxicity, and subacuter dermal toxicity in animals (rabbits). Tests for topical irritancy and topical and systemic sensitivity in man should be performed if such data are not available. Acceptable methods for testing for irritancy and sensitivity are described by Kligman and by Shelanski and Shelanski (Refs. 3 and 4).

Data on systemic absorption, distribution, metabolic fate, half-life, rate of excretion, and possible cumulative effects should be supplied wherever indicated in the ingredient statements discussed elsewhere in this document. (See part III. paragraph B.3. above—Category III active ingredient.)

a. *Recommended toxicological studies.* The Panel used data on "complaints per unit sold" submitted by the various companies as one of the criteria for evaluating human safety of ingredients and combination products. However, anecdotal descriptions of toxicity were not given serious consideration.

A variety of toxicological methods may be used to obtain data substantitating that a preparation is safe manufacturers are expected to conduct studies using the first five methods listed below. Methods 6 through 8 may be used to augment and confirm data obtained using methods 1 through 5. The Panel recognizes that better testing methods may be developed in the future. The requirements listed below will not preclude use of such methods in the event that they become available.

b. *Preclinical animal studies.*

(1) Acute oral LD_{50} toxicity in rats.

(2) Acute eye irritation in rabbits.

(3) Primary skin irritation and corrosivity in rabbits.

(4) Acute dermal toxicity in rabbits.

(5) Phototoxicity and photosensitization studies.

(6) Acute toxicity of inhaled aerosols and sprays in rats.

(7) Subacute dermal (21-day) toxicity in rabbits.

(8) Skin sensitization in rabbits or other suitable test animals.

c. *Safety studies in man.* A number of patch test methods have proven valuable in predicting skin irritancy and sensitization. These involve the use of occlusive dressings impregnated with the drug applied at various time intervals to selected sites in the subject's skin, allowing rest periods for possible sensitization to develop. Responses occurring within several days are indicative of irritancy. These areas are then challenged with the test drug after rest periods to determine whether sensitization has occurred. The Panel recommends the use of one of the following methods:

(1) The Draize human skin irritancy and sensitization tests and its various modifications utilizing the subject's back or arm may be used (Ref. 5).

(2) The method of Shelanski and Shelanski (Ref. 4) is one in which the active ingredient or formulation is applied regularly to the test site for 3 to 4 weeks. Then, following a rest period of 2 weeks, there is a single challenge application of the drug or formulation (Ref. 4). The early applications are to detect primary skin irritants and initiate sensitization in susceptible persons. The challenge dose is to detect skin sensitizers.

(3) The maximization procedure of Kligman or its modifications uses an irritant on the test site, therby hastening and accentuating the skin-sensitizing potential of a substance (Ref. 3).

The effectiveness of certain ingredients can be correlated with the degree of percutaneous absorption, which may also be correlated with systemic and local toxicity. Studies on penetration of drugs through the skin of animals unfortunately cannot be extrapolated to man. Some drugs are absorbed in excessive quantities if applied to large surface areas of the body. The degree of absorption or penetration may be determined by studying blood levels and measuring the total quantity excreted. Inferences of safety may be based on the observed drug levels and their correlation with toxicity studies.

The Panel considers certain in vitro studies applicable for establishing criteria for safety and effectiveness. The method of Fritsch and Stoughton is an example of an in vetro method in which excised human skin is used for studies on penetration (Ref. 6). Studies utilizing the friction blister, suction blister, sunburn blister, blister caused by freezing skin with liquid nitrogen, dermatome specimens, and excised skin are acceptable. Drug penetration through a blister top may be determined by analyzing the blister fluid. In addition, the top of the blister may be excised and analyzed quantitatively for

the drug to determine the degree of absorption into the skin layers.

Topical anesthetics, topical analgesics and topical antipruritics, once through the epithelial barrier, pass into the tissue fluids beneath, into the venules and lymphatics and are distributed to various tissues, particularly those that are capillary rich. Some esters of topical anesthetics, such as tetracaine, are hydrolyzed by plasma esterases into the alcohol and acid from which they were formed, and are thereby inactivated. The amide type of topical anesthetic is not altered by esterases but ultimately passes from the blood and tissues to the liver, where it undergoes biodegradation (detoxification). The byproducts are eliminated into the urine. Topical anesthetics that are not hydrolyzed by plasma esterases or easily detoxified by the liver, such as dibucaine or cocaine, are eliminated unchanged by the kidney. Alcohol-type topical anesthetics are not affected by the plasma esterases. They are detoxified by the liver through various types of chemical reactions, such as oxidation, reduction, conjugation, or transfer reactions. Unmetabolized portions are excreted into the urine.

Solvents and other substances used to formulate a finished product that penetrates the barriers are detoxified in the same manner as the active ingredients. It is possible for highly lipophilic substances that are used daily for long periods of time to accumulate in the adipose and other lipid-rich tissues, particularly if they are not readily biodegradable, where they may remain for days, weeks, or months (Refs. 7 and 8). None of the ingredients the panel has evaluated is retained for long periods of time in adipose or lipid-rich tissues. Methods to detect minute quantities of some substances are not available, and in general, no standard procedure to measure skin penetration in humans exists. Animal studies should be performed as a preliminary to human in vivo testing (Ref. 2).

Note.—The above considerations pertain to all external analgesics. The following two sections deal with methods of evaluating analgesics, anesthetics, and antipruritics, on the one hand, and counterirritants, on the other.

5. *Evaluation of analgesics, anesthetics, and antipruritics.* Anesthetics, analgesics, and antipruritics produce their effects by depressing cutaneous sensory receptors or by the removal of noxious stimuli that induce pain. Corroborating data for many ingredients and preparations evaluated by the Panel can be obtained by inducing pain experimentally in normal volunteers. Methods for inducing experimental pain are described below, as are methods for measuring the intensity of pain. Some of these methods are suitable for determining effectiveness of analgesic ingredients on both the intact skin and damaged skin. Data obtained using these ingredients to relieve experimentally induced pain are acceptable as corroborating evidence only, but data from clinical studies must be submitted in support of an evaluation. Although the general comments outlined above for preparation of protocols are applicable to this group of ingredients, certain modifications or additional comments are necessary in obtaining data for evaluation of anesthetics, analgesics, and antipruritics.

a. *Mode of application.* The Panel emphasizes that the mode of application of the ingredient under study is an important consideration and should be specified in the evaluation report. Some preparations are merely applied, without rubbing or massaging, in the form of a film on the intact skin or over a lesion where the skin is not intact. Rubbing and massaging may accelerate the absorption as much as 24 to 50 percent (Ref. 9).

The frequency of application should be recorded. Data obtained following a single application cannot be used to substantiate claims made when a preparation is intended for multiple applications.

b. *Studies on the damaged or abraded skin.* The Panel stresses that there is considerable difference between studies performed on intact skin and those performed on skin that has been damaged as a result of injury, trauma, disease, or other causes. When an ingredient is applied to the abraded skin, the avenues of access for an active ingredient to subepidermal structures are open and absorption occurs readily. Contact, therefore, is readily made with the terminal receptors that subserve pain and itch and other sensations. If the agent is of sufficient potency, anesthesia may result.

The minimum effective concentration on the damaged abraded skin is less than it is on the intact skin. The "horny layer" or dermis provides an effective barrier, through which drugs, chemicals, or noxious agents are not able to pentrate unless they are of a lipophilic nature (Refs. 9 and 10). The stratum corneum, the outer horny layer of the epidermis, is made of dead, keratinized cells that have lost their nuclei in the process of keratinization. They maintain their physiologic connection with neighboring cells through bridges called desmosomes. This layer of keratin acts as a barrier and protects humans from the environment (Ref. 9).

The stratum corneum is strongly hydrophilic. The amount of water in this layer depends mostly on the moisture content of the environment and partly on the water supply available from the body itself. This water-holding capacity of keratin confers upon the skin its property of suppleness (Ref. 9). Substances soluble in both water and lipids readily and easily pass through this layer. Damage to, or removal of, the stratum corneum allows practically any molecule, regardless of size, to pass through the skin (Ref. 9). Meaningful data can be obtained by abrading the skin of normal volunteers and studying the effect of topical analgesics, anesthetics, and antipruritics on these areas. The techniques that can be used are described below.

c. *Evaluation of analgesic and antipruritic agents exerting anti-inflammatory effects.* The Panel also recognizes that the methods described below may not be suitable for evaluating the effectiveness of analgesic and anitpruritic drugs that do not block nerve fibers and prevent transmission of nerve impulses, such as the anti-inflammatory agents. The steroids, antihistamines, and other drugs are anti-inflammatory agents that act by reducing edema and alleviating pressure on cutaneous receptors that incite the sensation of pain. The Panel recommends in these instances that studies of these products be performed on patients with edema of the skin and inflammatory conditions using the protocol described above. (See part III. paragraph C.1. above—General considerations.)

d. *Methods of studying salts of bases.* Some active ingredients considered by the Panel are bases but are present in the formulation in the form of a salt, or the media in which they are incorporated are acidic and convert the bases to salts. The salts do not penetrate the intact skin because they are ionized and are not lipophilic (salts of lidocaine, tetracaine, dibucaine, etc.) (Ref. 10). In most instances, these salts have been placed in Category I for use on the damaged, excoriated, or abraded skin because they readily come into contact with the nerve endings in the tissues and are effective for relief of pain and itching on the skin.

It is the opinion of the Panel that these ingredients that are active as bases on the intact skin, but are not active as salts, could be buffered or neutralized and converted to bases. The finished product could be reformulated to contain the concentration of the ingredient that is effective. The salt may

be effective at a higher concentration than is present in the formulation, in which case the concentration may have to be increased to the effective level. In either case, efficacy and safety studies that meet the criteria in the above guidelines should be conducted. The concentration of active ingredients that are present in less than the minimum concentration considered to be effective by the Panel should be increased to the minimum effective concentration in the formulation (Ref. 10).

e. *Techniques of algometry*—(1) *Biologic methods.* Biologic methods have been used in laboratory studies to assess the effectiveness of analgesics. The Panel does not require such studies, but if they are available, they may assist in evaluation of the ingredient. For example, solutions of known concentrations of analgesics have been applied to the skin of the limbs of frogs (Ref. 11). The areas are tested with a physical or chemical stimulus of known intensity, and the motor responses are observed. In one method, a paper disk impregnated with a known concentration and volume of acetic acid is applied to the skin, and the effect upon the withdrawal of the extremity is observed. Other amphibia and reptiles have been immersed in solutions of anesthetic or analgesic agents, and the responses to reflex stimulation have been observed and quantitated. The skin of the frog, however, is vastly different from that of humans and other mammals, both in histologic structure and absorptive capacity. Therefore, these data cannot be extrapolated to humans and are only supportive.

The cornea of the rabbit or guinea pig likewise is often used as a test site for topical anesthetics. The disappearance of the blink reflex in the eye after application of a stumulus of known intensity yields data that are considered to be objective. Tests on the cornea of animals, again, are by themselves not meaningful because the surface of the cornea cannot be likened to human skin. Such data are merely supportive and must be accompanied by data on humans.

(2) *Methods used in humans.* Pain may be superficial or deep. It may be elicited by thermal, mechanical, electrical, or chemical stimuli. The impulses that incite cutaneous pain and itch are carried by the same fibers and can be reproduced by varying the intensity of a stimulus. Therefore, the methods described below are useful for studying both pain and itch.

(i) *Stimulation using radiant heat.* Some investigators have used the Hardy-Woolf-Goodell pain threshold apparatus as a source of painful stimuli (Refs. 12 and 13). The apparatus described in the literature consisted of a calibrated radiometer that provided a thermal stimulus to the skin. The source of energy was a 1,000-watt incandescent lamp, a condensing lens that permits the rays to be focused on the areas to be tested, and a rheostat to vary the intensity of the beam. Test areas approximately 3.5 cm in diameter were blackened with some form of finely pulverized purified carbon, such as carbon black or a suspension of India ink. This insured complete absorption and conversion of the radiant energy to heat and prevented penetration of the rays below the surface of the skin. The effects of pigmentation of the skin were also eliminated. The subject verbally reported what sensation was experienced at the end of a particular interval of time. Usually a 3-second exposure with a standard beam intensity was necessary to evoke a sensation of pricking, pain, itching, or burning and was considered to be the least perceptible stimulus, and therefore, the pain threshold.

In using this method, results are best obtained by approaching the pain threshold by using two or three subminimal stimuli. Thus, overstimulation of a test area is avoided. Such overstimulation may cause subsequent hypalgesia (decrease in the sensation of pain), which could alter the absorption of the agents being tested due to injury of the skin, even though the skin remains intact. The blackened areas are coated with the preparations to be studied , including one which contains only the medium used for incorporating the active ingredients. This, therefore, serves as a control. The subjects should be unaware of the composition of preparations applied to a particular area. Sensations of warmth or coolness, if they are caused by one of the ingredients, may prevent the test from being completely blind because they may stimulate sensory receptors other than those of pain. The subject is, therefore, able to identify the preparation on reapplication or retesting and to distinguish it from other preparations and the control. Blind studies may be performed only if neither the subject nor the individual interpreting the responses to the stimuli knows the nature of the preparation that has been applied over the test area. The material may be applied by a third person who knows its identity or it may be coded so that no one knows its identity. The code is broken after the tests are complete. Thus, such an experiment can be considered blind, particularly if none of the ingredients evokes sensations other than analgesic or antipruritic. Enough data should be obtained for statistical analysis.

The objection to this technique is that the thermal stimulus may elicit a response from receptors subserving warmth, rather than those subserving pain and itch. Furthermore, the application of carbon black and the heat from the radiant energy may change the water content of the skin, and thereby alter its absorptive capacity during the experiments.

(ii) *Method using pricking as a stimulus.* Monash (Ref. 14) devised several topical analgesic testing methods that permit the continuous application of a test solution. The testing was done by pricking with a sharp instrument. A ball of absorbent cotton approximately 1 cm in diameter soaked with the desired solution was placed on the skin and covered with waxed paper or cellophane and then fixed in place with adhesive plaster. thirty minutes later the cotton was removed and the area pricked with a sharp instrument to determine whether anesthesia was present. If not present, the cotton was then again soaked with the solution and reapplied. The testing was performed at 15-minute intervals. When anesthesia was complete, the patch was removed and the duration of anesthesia determined by subsequent testing at 15- to 30-minute intervals.

The chief objection to this technique is that the agents are not ordinarily applied to the skin in this manner. Furthermore, it is difficult to quantitate the intensity of the stimulus by merely pricking the surface, unless the study is designed to observe only the anesthetic effect, and not the analgesic effect, of a preparation. The method tests for anesthesia, partial or complete blockade, or hypalgesia, but does not test for analgesia in cases where relief of burning or itching is obtained without the patient experiencing numbness. Pricking does not evoke a sensation of itch, because itch is evoked by subminimal stimulus while the nerve endings still remain partially active and are able to perceive pain. However, this method is useful in determining whether percutaneous absorption of topical anesthetic bases and salts occurs.

(iii) *Electrical stimulation.* Electric currents have been used to evoke the sensation of pain and itching on the skin. Hardy et al. (Ref. 12) note that the first recorded use was that by Macht et al. in 1916, who applied faradic current to the scrubbed skin of the dorsum of the hand and determined the increase in the pain threshold after the application of cocaine and certain opium alkaloids.

Dalili and Adriani (Refs. 10 and 15) have recently devised a method utilizing a pulsatile alternating current delivered from a Grass 44 Model stimulator that selectively activates the receptors in the cutaneous nerves that subserve pain and itch. A subminimal stimulus evokes a sensation of itching and burning (Ref. 16). Increasing the intensity of the stimulus induces pain. Further increases cause the current to penetrate the subcutaneous structures and stimulate the motor fibers, producing muscle contraction, twitching, and cramping. A pulsatile current consisting of sine waves of 30 cycles per second of 5 milliseconds duration with 2-millisecond periods of silence between impulses is used. Repeated stimulation reproduces a sensation of itching and pricking without apparent injury to the cutaneous structures. A pinpoint metal tip is necessary as the exploring electrode. The type of electrode used is important because current density becomes a factor. The minimal quantity of current that, when localized over a small area of pinpoint size, is effective in causing a stimulus fails to evoke a response when applied over a wider area. From 25 to 40 volts are generally necessary to deliver the required amperage. This is due to the variation of the resistance of the skin in different subjects. The resistance of the skin varies from subject to subject and even in the same subject at different times. The threshold of excitation may be reduced to 0.3 milliampere by pinpointing the contact area with the fine tip of the electrode. The necessary amperage varies from subject to subject, ranging from 1 to 10 milliamperes, but remains constant for each subject and for the same subject in each period of testing.

Adriani and Dalili (Ref. 10), as well as the investigators using the thermal stimulation technique described above, selected the volar surface of the forearm as the test site. An indifferent electrode is fixed to the dorsum of the forearm over gauze soaked in saline. Control values are established at multiple points over the test site, which measures from 5 to 7.5 cm^2. The preparation under investigation is applied for 30 minutes. Areas 1 x 1 cm are wiped dry at 15-minute intervals and stimulated for 1- to 2-second intervals until itching is perceived. Generally 1 hour elapses before the entire area is wiped and tested. A single application for 60 minutes established the clinical usefulness of a preparation. At is the case with other workers, test sites coated with a placebo are used as controls. One possible objection to this method is that a stimulus greater than is necessary to cause itch may be applied, causing tingling, which may be misinterpreted by some subjects.

Adriani and Dalili (Ref. 10) produced ultraviolet light burns using a GE Model 1F2 lamp held 60 cm from the volar surface of the forearm for 8 to 18 minutes and tested the effectiveness of various agents in relieving the discomfort. Patients not complaining of itching and burning after developing erythema and not experiencing hypersensitivity to touch were excluded from study. Obviously, data obtained in such a study are subjective because reliance must be placed upon the patient's interpretation of the degree of the degree of relief obtained. A xenon lamp may be used to provide radiation of known and fixed wavelengths, as would be the case in evaluating sunscreens, but is not necessary. Thus, studies could be simultaneously performed on both the injured intact skin and the intact skin. Efficacy is determined subjectively by questioning the subject on the degree of the relief of the ensuing discomfort. Responses to electrical stimulation are graded 0 if no relief of discomfort resulted, 1+ if a partial block is obtained, or 2+ if no itching or burning occurs from the electrical stimulation. Painful tingling or vibratory sensations result if the current is increased beyond the control value or if the intensity of the current is increased when a blockade is obtained. These workers also noted that in some cases subjects complained that an aggravation of discomfort resulted after application of the preparation. This increase in discomfort has been termed "antianalgesia." Tests of such a response were recorded and coded as E. In addition, the subject's evaluation of the relief of discomfort on the injured skin was graded as 0 if no relief of symptoms resulted, 1+ if the relief was partial, and 2+ if there was complete relief of itching, pricking, and burning (Ref. 15).

(iv) *Using intradermal wheals as test sites.* Adriani and Dalili (Refs. 10 and 15) also infiltrated successive strata of the epidermis with 0.01 to 0.02 mL of a soluble topical anesthetic with the 30-gauge needle of a tuberculin syringe. Stimulation over the treated area with the electric current no longer caused itching and burning. Increasing the amperage and voltage elicited vibratory and tingling sensations, indicating that the current acted on receptors of different types. The nerves in the deeper layers of the skin and muscle apparently were not blocked and were stimulated.

Data in which studies have been performed using an intradermal wheal are of no value in support of a submission that makes claims for therapeutic effectiveness of a particular ingredient when applied topically to the intact skin. An ingredient applied in this manner is introduced beneath the stratum corneum into the stratum germinativum, where it is readily bioavailable and comes into contact with the nerve endings in the skin and produces anesthesia. Some investigators have used such data to support claims for effectiveness of topically applied preparations. The area over the wheal is not responsive to pricking or other forms of stimulation because complete anesthesia ensues.

(v) *Additional methods for inducing experimental pain.* It has been indicated above that induced pain differs from pathologic pain due to trauma or disease (Ref. 14). Tests of the effectiveness of analgesics in the laboratory using experimentally induced pain may not coincide with the results obtained when pain is of pathologic origin. Fortunately, the situation is different as far as the skin is concerned, because pain of pathologic origin can be produced by thermal injury or by abrading the skin.

Burning with ultraviolet light has been described above in the section on electrical stimulation. Adriani and Dalili (Ref. 10) used a template which has six openings to permit specific areas to be exposed to ultraviolet radiation to cause a burn on the forearm. This results in six areas for use as test sites. At least five ingredients and a placebo may be used simultaneously. If both arms are used, this permits the testing of 10 preparations, or a cross-over technique, if so desired.

Although many techniques are available for producing abraisons and disrupting the skin for investigational purposes, the most popular, the least traumatic, and most commonly used method is that in which sticky tape is used for excoriation of the skin. The tape is applied over the desired area and removed 10 to 15 times in succession. In the process, the epidermis is disrupted and the stratum corneum is removed, thereby breaking the integrity of the epitherlial barrier. Burning sensations can be elicited by application of dilute alcohol or citric or acetic acid solutions to the abraded area, after which the analgesic is applied.

Another method that has been used for causing very fine abraisons of the skin is to apply cowhage (itch powder) to an area of the skin. Cowhage is derived from a tropical woody vine covered with barbed hairs that, when applied to the skin, cause intense itching. Tests using cowhage are valid if the experiment is designed to test the

effectiveness of a preparation on the damaged skin, but not on the intact skin. The fact that the agents are absorbed easily following such treatment and exert a topical anesthetic or hypalgesic effect must be recognized. They are not acting through intact skin.

(vi) *Abrading the skin.* Vigorous scrubbing with a brush may also be used as a method of abrading the skin. Abrasions may be obtained by rubbing the skin with a fine grade of sandpaper or other abrasive material. These techniques are not only less acceptable to volunteers than stripping, but are also less controllable.

Application of an ingredient that is only analgesic on the intact skin may produce total anesthesia on the damaged or abraded skin (Ref. 12). This can be easily tested by pinpricking, radiant heat, electric current, or application of chemicals that cause stinging but no injury. In some cases the agent is not sufficiently potent, and partial anesthesia or, more accurately, hypalgesia is obtained. Testing on abraded skin is considerably less subjective than methods for resting the effects of drugs on the intact skin.

(3) *Selection of test sites.* The thickness of the skin is an important consideration in conducting investigations of topical anesthetics and analgesics. Thickness of all layers varies from one are of the body to another. The epidermis, particularly the stratum corneum, is thickest in the soles and the palms (Ref. 9). Penetration and absorption are poorest at these sites because the outer, horny keratin layer is dense in these areas and the stratum lucidum, which is thin in other areas of the body, is well defined beneath the stratum corneum. In most cases, investigators have used the volar surface of the forearm as the most convenient site for testing. This area is most amenable for the quantiation of the degree of analegsia and anesthesia. The thickness of skin in the volar surface appears to be less than it is in most areas of the body (Ref. 9). And because the number of hair follicles and sebaceous glands in this area is sparse compared with other areas of the body, any absorption or penetration that occurs via the hair follicles and other appendages in the skin is reduced. Most investigators doubt that the therapeutic effects obtained from these ingredients are due to absorption along the hair follicles and from the sebaceous glands. Ample evidence exists that absorption occurs directly through the stratum corneum (Ref. 9).

The selection of the test site area is important because the number of terminal nerve endings per cm^2 of skin varies from one area of the body to another. Meaningful data may not be obtained if an area of low pain sensitivity is selected.

Mucocutaneous junctions as test sites: Studies performed at test sites utilizing mucocutaneous junctions are not acceptable for obtaining data on the skin alone because preparations that are readily absorbed and effective on the mucous membranes are not necessarily absorbed and effective on the skin. Data obtained by applying analgesics and anesthetics at the lips, nares, anorectal areas, and the female genitalia are not suitable except in instances whre the product is intended to be applied to these areas (Refs. 10 and 15).

(4) *Use of other or new techniques.* The Panel recognize that there is a dearth of methods for determining the analgesic effects on the skin and that other methods may be developed in the future. The determination of the degree of penetration of a radioactive ingredient into the skin has been suggested as one possible technique. However, the fact that a drug penetrates the skin does not necessarily mean that it is effective as a topical analgesic. It is doubtful that this technique will yield data of value. Systemically administered drugs that produce itching could be used but are not practical at this time. Morphine exerts such an effect. Morphine, however, is not the agent of choice, nor does it produce itching in all subjects to whom it is given. Morphine apparently acts peripherally to reduce the threshold for itch, even though centrally it elevates the threshold for pain. The analgesic effect may counterbalance the pruritic effect, and no sensation of itch may result. Methods utilizing pressure or ischemia are suitable for evaluating deep pain but not cutaneous pain. Although other methods and techniques are available for use in evaluating pain, they are too detailed to discuss in this document.

6. *Evaluation of counterirritants and claims for deep-seated pain.* a. *Introduction.* The methods described above are intended to evaluate anesthetics, antipruritics, and drugs that produce analgesia by depressing cutaneous sensory receptors, and are not applicable in evaluating the effectiveness of analgesics that stimulate cutaneous sensory receptors and exert their effects by counterirritation. The Panel recogizes that methods are not available for experimentally inducing pain of the type relieved by counterirritants. Investigators cannot rely upon normal subjects to obtain data to evaluate effectiveness. The Panel, therefore, recommends that studies be performed on patients with pathologic pain with well-defined discomfort involving the musculo-sketetal system, such as arthritis, tendonitis, bursitis, myositis (traumatic or otherwise), neuritis, strains, sprains, related syndromes, or deep-seated skin. The general comments on the selection and treatment of subjects for study, the evaluation of data, the establishment of dose-effect relationships, labeling, etc. are also applicable to drugs acting by counterirritations. Studies on patients are to be conducted as described below.

If possible, studies should be double-blind. Patients who have similar types of disorders should be randomly selected for treatment, divided into two groups, and the groups compared. One group is treated with the drug being tested and another group with the vehicle alone, suitably controlled. The disease process for which the testing is done should have the same etiology. For example, when tests are performed on patients with arthritis, all patients should have the same type of arthritis, i.e., rheumatoid, osteoarthritis, etc. The cross-over technique may be used when the condition under study is chronic and only temporary symptomatic relief is obtained by application of the medicament. The cross-over technique is not suitable in subjects who experience partial improvement of symptoms after application of a medicament or in self-limiting conditions. A minimum of 25 subjects should be tested with the drug and 25 with the suitable vehicle for each type of syndrome by two independent investigators in single sequence methodology. In cross-over studies, 25 subjects altogther are sufficient. The effects could be evaluated on at least two types of painful disorders, e.g., arthritis, bursitis, myositis, tendonitis, and traumatic injuries. The mode of application of the drug must be specified and should be uniform in a particular clinical trial. The data on testing should include application frequency, as specified in the labeling, for not less than a 48-hour period. A washout period of at least 12 hours should be used in cross-over studies (Ref. 2).

b. *Methods of evaluation.* The following subjective and objective methods of evaluation are available to determine the effectiveness of analgesics that act by counterirritation:

(1) *Evaluation of the effects on pain.* Certain musculoskeletal disorders are accompanied by inflamation that causes swelling, tenderness, and redness, as well as pain. A description of the type of pain relief should be recorded and the degree of relief based upon an

applicable scoring system, as for example, 0 = none, 1 = slight, 2 = moderate, and 3 = complete. The scores should be evaluated statistically and values compared with those obtained from treatment with a placebo vehicle control. The Panel recognizes that the inflammatory process may not recede, but the preparation may cause varying degrees of pain relief and such data is acceptable (Refs. 13 and 17).

The presence of erythema and its intensity, and the appearance of edema (indurated, pitting, or soft) may be parameters that could be objectively evaluated and correlated with the degree of relief of pain and changes mentioned above.

(2) *Effects on range of motion of joints.* The range of motion in degrees should be determined using a protractor or other device acceptable for mensuration of angles. Pretreatment values should be established for both active and passive movement and changes in the degree of extension, flexion, adduction, or abduction of a limb. This data should be accompanied by a description of the type and intensity of pain and degree of pain relief during each maneuver before and after treatment. The degree of pain should be rated on an acceptable scoring system as described above.

Measurements of the effect of the medication on motion should be made at sufficiently frequent intervals to determine the onset of analgesic effect, duration, degree of pain relief, and time of return of syptoms. Measurements should be objectively made. The technique of measurement should be consistent throughout the study and made by the same observer throughout a trail period. The Panel recognize that counterirritant analgesics are not curative and may cause no improvement in mobility of the joints or limbs but may still relieve pain and provide comfort as long as there is no attempt to move a limb or an extremely. Subjective data on pain relief are acceptable. The Panel also recognizes that although motion may not be restricted, pain will be elicited when a muscle or joint is activated voluntarily or moved passively, and that a topically applied medication may relieve such pain on movement of an extremity or a limb. In these instances, subjective data will be accepted by the Panel.

(3) *Effects of pressure or palpation on musculoskeletal pain.* Pain can be induced by using an inflatable cuff that exerts pressure on a metal or plastic plate over the affected area. The pressure in the cuff is measured by a manometer. The amount of pressure necessary to inflate the cuff to elicit pain is an indicator of the relief obtained. The degree of pain should be based upon subjective response conceptions (Ref. 18). Pretreatment readings are established, and the variations in pressure noted at necessary intervals established by the observer. Pressure induced by adding a series of weights or applying pressure with a loaded spring could also be used.

(4) *Relief of muscle spasm.* Hypertonus or muscle spasm accompanies musculoskeletal disorders to protect an affected part by splinting. Changes in muscle tone may be detected by use of the electromyograph. Pretreatment electromyographic values followed by measurements at appropriate time intervals may be instituted to determine the relief of spasm. If such studies are undertaken, these should be correlated with the degree of range of motion and the subjective evaluation of degree of pain relief mentioned above (Refs. 19 and 20).

(5) *Measurement of skin temperatures.* Topical analgesics which stimulate cutaneous receptors, send impulses into central receptors that excite centers that control the caliber of the blood vessels and reflexly cause vasodilation. An increase in blood flow results over the area of application of the medicament and in the vessels in the skin area subserved by the spinal segment receiving these cutaneous impulses. An increase in skin temperature results, which can be detected by using a thermocouple, thermistor, or other device that detects changes in skin temperature. An increase in skin temperature is not proof of efficacy but does provide confirmatory evidence with other data obtained and the subjective responses of the patient that a drug is exerting a pharmacologic effect.

(6) *Blood plasma levels.* Certain analgesics with counterirritant effects may be absorbed percutaneously and disseminated to the tissues, where they may exert an anti-inflammatory effect that is presumed to produce analgesia. Other effects may be produced. The Panel could accept data to support effectiveness of an ingredient as a topical analgesic if the action is systemic and not topical in the skin.

Method (1) or (2) or (3) discussed above is mandatory and must be used in the evaluation of the effectiveness of an ingredient. Methods (4), (5), or (6) are optional methods that may be used in support of the results obtained from any one of the above tests.

7. Summary outline of required testing. The following outline summarizes the tests required to reclassify a Category III active ingredient to Category I status:

a. *Studies required to demonstrate safety.* The following studies are required to reclassify external analgesic active ingredients classified as Category III for safety considerations:

(1) *Preclinical studies.* The required preclinical studies have been discussed in detail elsewhere in this document. (See part III. paragraph C.4.a. above—Recommended toxicological studies.)

(i) Animal toxicity studies.

(ii) Skin irritancy, dermal toxicity, and phototoxicity and photosensitization studies in animals.

(2) *Clinical studies.* Irritancy and sensitization studies in humans, utilizing the patch tests, are required.

b. *Studies required to demonstrate effectiveness.* (1) The following clinical studies are required to reclassify all topical analgesic, anesthetic, and antipruritic active ingredients classified as Category III for effectiveness:

(i) When possible, one double-blind study on a minimum of 25 normal human subjects (volunteers) demonstrating topical analgesic effects of the final formulated product using one or more of the algesimetric methods discussed above. The test sites should be those areas of the skin known to be richly endowed with terminal painperceiving nerve endings.

(ii) When possible, one double-blind study on a minimum of 25 subjects with pathologic cutaneous lesions that cause pain, burning, or itch. The dose-response relationship should be established indicating the range between the minimum effective dose and the maximum safe dose. Where applicable, a comparison between the effects on the intact skin and the effects on damaged skin should be included in the study. The study should be done using the final formulated product and a placebo.

(iii) Where using the studies described above is not applicable, as with active ingredients that act by exerting an anti-inflammatory effect, when possible, double-blind studies should be done in a minimum of 25 subjects with edema or inflammatory disturbances of the skin that are as similar as possible and are at approximately the identical test site in all subjects. The studies should be done using the final formulated product and a suitable vehicle. The dose-response relationship should be established indicating the range between the minimum effective dose and the maximum safe dose. Where applicable, a comparison between the effects on the intact skin and the effects on damaged skin should be included in the study.

(2) The following clinical studies are required to reclassify all topical

counterirritant active ingredients classified as Category III for effectiveness: When possible, double-blind studies on a minimum of 25 subjects using the ingredient and a suitable vehicle for a control for 2 different types of painful disorders and evaluation with methods (1), (2), or (3) described above. Tests should be performed by two independent investigators for each of the painful disorders studied.

References

(1) Beecher, H. K., "Measurement of Subjective Responses: Quantitative Effects of Drugs," Oxford University Press, New York, 1959.

(2) Modell, W., H. Schild, and A. Wilson, "Applied Pharmacology," W. B. Saunders Co., Philadelphia, pp. 21–47, 1976.

(3) Kligman, A. M., "The Identification of Contact Allergens by Human Assay III. The Maximization Test: A Procedure for Screening and Rating Contact Sensitizers," *Journal of Investigative Dermatology,* 47:393–409, 1966.

(4) Shelanski, H. A. and M. V. Shelanski, "A New Technique of Human Patch Tests," *in* "Proceedings of Scientific Section of the Toilet Goods Association," 19:46–49, 1953.

(5) Draize, J. H., "Appraisal of Safety of Chemicals in Foods, Drugs and Cosmetics," The Association of Food and Drug Officials of the United States, Texas State Department of Health, Austin, Texas, pp. 46–59, 1959.

(6) Fritsch, W. C. and R. B. Stoughton, "The Effect of Temperature and Humidity on the Penetration of C^{14} Acetylsalicylic Acid in Excised Human Skin," *Journal of Investigative Dermatology,* 41:307–310, 1963.

(7) Modell, W. H., Schild, and A. Wilson, "Applied Pharmacology," W. B. Saunders Co., Philadelphia, pp. 41–44, 145–154, 1976.

(8) Adriani, J. and M. Naraghi, "Pharmacologic Basis of Regional Pain Relief," *Annual Review of Pharmacology and Toxicology,* 17:223–242, 1977.

(9) Criep, L. H., "Dermatologic Allergy," W. B. Saunders Co., Philadelphia, pp. 3–30, 1967.

(10) Adriani, J. and H. Dalili, "Penetration of Local Anesthetics through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–841, 1971.

(11) Regnier, J., R. Quevauriller, and L. Fornault, "Measurement of the Activity of Anesthetics by the Frog Skin Method," *Anesthesia and Analgesia,* 5:555–557, 1939.

(12) Hardy, J. D., H. G. Wolff, and H. Goodell, "Studies on Pain. A New Method for Measuring Pain Threshold: Observations on Spatial Summation of Pain," *Journal of Clinical Investigation,* 19:649–658, 1940.

(13) Wolff, H. G. and S. Wolf, "Pain," Charles C. Thomas Publishing Co., Springfield, IL, pp. 3–10, 1958.

(14) Monash, S., "Topical Anesthesia of the Unbroken Skin," *Archives of Dermatology,* 76:752–756, 1957.

(15) Dalili, H. and J. Adriani, "The Efficacy of Local Anesthetics in Blocking the Sensations of Itching, Burning, and Pain in Normal and 'Sunburned' Skin," *Clinical Pharmacology and Therapeutics,* 12:913–919, 1971.

(16) Graham, D. T., H. Goodell, and H. G. Wolff, "Itch Sensation in the Skin: Experimental Observations of the Neural Mechanisms Involved," *in* "Proceedings of the Association for Research in Nervous and Mental Disease," The Williams and Wilkins Co., Baltimore, 1950.

(17) Kolodny, A. L. and P. McCloughin, "Comprehensive Approach to Therapy of Pain," Charles C. Thomas Publishing Co., Springfield, IL, pp. 27–33, 1966.

(18) Beecher, H. R., "The Powerful Placebo," *Journal of the American Medical Association,* 159:602, 1955.

(19) White, J. R. and J. M. Sage, "Effects of a Counterirritant on Muscular Distress in Patients with Arthritis," *Physical Therapy,* 51:36–42, 1971.

(20) White, J. R. and J. M. Sage, "Topical Analgesic on Induced Muscular Pain," *Physical Therapy,* 50:166–172, 1970.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 348, to read as follows:

PART 348—EXTERNAL ANALGESIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—[Reserved]

Subpart D—Labeling

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 348.1 Scope.

An over-the-counter external analgesic product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions on this Part 348 and each of the general conditions established in § 330.1 of this chapter.

§ 348.3 Definitions.

(a) *Age.* Infant (under 2 years of age), child (2 to under 12 years of age), and adult (12 years of age and over).

(b) *Cutaneous sensory receptor.* A sense organ that is connected to the terminal fibers of a network of nerves in the skin for the perception of pain, itching, cold, warmth, touch, and pressure.

(c) *External analgesic.* A topically applied drug that has a topical analgesic, anesthetic, or antipruritic effect by depressing cutaneous sensory receptors, or that has a topical counterirritant effect by stimulating cutaneous sensory receptors.

(d) *Topical analgesic.* An externally (topically) applied drug that, by depressing cutaneous sensory receptors, relieves pain without necessarily abolishing other sensations, or that causes partial blockades of subcutaneous terminal nerve endings so that a minimal stimulus evokes no painful response, but a greater stimulus does.

(e) *Topical anesthetic.* An externally (topically) applied drug that completely blocks pain receptors, resulting in a sensation of numbness and an abolition of responses to painful stimuli by depressing cutaneous sensory receptors.

(f) *Topical antipruritic.* An externally (topically) applied drug that relieves itching by depressing cutaneous sensory receptors.

(g) *Topical counterirritant.* An externally (topically) applied drug that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints, or viscera distal to the site of application by stimulating cutaneous sensory receptors.

Subpart B—Active Ingredients

§ 348.10 External analgesic active ingredients.

The external analgesic active ingredients of the product consist of the ingredients identified below, within the concentrations established.

(a) *External analgesic active ingredients that stimulate cutaneous sensory receptors (counterirritants).*

(1) Allyl isothiocyanate 0.5 to 5.0 percent.

(2) Ammonia water, stronger 1.0 to 2.5 percent.

(3) Camphor exceeding 3.0 percent up to 11 percent.

(4) Capsaicin 0.025 to 0.25 percent (or the equivalent amount of capsaicin in capsicum or capsicum oleoresin).
(5) Histamine dihydrochloride 0.025 to 0.10 percent.
(6) Menthol exceeding 1.25 percent up to 16 percent.
(7) Methyl nicotinate 0.25 to 1.0 percent.
(8) Methyl salicylate 10 to 60 percent.
(9) Turpentine oil 6 to 50 percent.

(b) *External analgesic active ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics.*
(1) Benzocaine 5 to 20 percent.
(2) Benzyl alcohol 10 to 33 percent.
(3) Butamben picrate 1 percent.
(4) Camphor 0.1 to 3.0 percent.
(5) Dibucaine 0.25 to 1.0 percent.
(6) Dibucaine hydrochloride 0.25 to 1.0 percent.
(7) Dimethisoquin hydrochloride 0.3 to 0.5 percent.
(8) Diphenhydramine hydrochloride 1 to 2 percent.
(9) Dyclonine hydrochloride 0.5 to 1.0 percent.
(10) Hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) 0.25 to 0.5 percent.
(11) Juniper tar 1 to 5 percent.
(12) Lidocaine 0.5 to 4 percent.
(13) Lidocaine hydrochloride 0.5 to 4 percent.
(14) Menthol 0.1 to 1.0 percent.
(15) Methapyrilene hydrochloride 1 to 2 percent.
(16) Phenol 0.5 to 2.0 percent.
(17) Phenolate sodium 0.5 to 2.0 percent.
(18) Pramoxine hydrochloride 0.5 to 1.0 percent.
(19) Resorcinol 0.5 to 3.0 percent.
(20) Tetracaine 1 to 2 percent.
(21) Tetracaine hydrochloride 1 to 2 percent.
(22) Tripelennamine hydrochloride 0.5 to 2.0 percent.

§ 348.20 Combinations of external analgesic active ingredients.

(a) *Combinations of external analgesic active ingredients that stimulate cutaneous sensory receptors (counterirritants).* (1) The active ingredients of the combination product consist of no more than one active ingredient from each of any two, three, or four of the following groups of counterirritant active ingredients when used within the concentrations identified in § 348.10(a):
(i) Allyl isothiocyanate, ammonia water, methyl salicylate, or turpentine oil.
(ii) Camphor or menthol.
(iii) Histamine dihydrochloride or methyl nicotinate.
(iv) Capsaicin, capsicum, or capsicum oleoresin.
(2) The active ingredients of the combination product consist of no more than one active ingredient from each of any one, two, or three of the counterirritant groups identified in paragraph (a)(1) (i), (iii), or (iv) of this section, and camphor and menthol when used within the topical concentration limits identified in § 348.10(a).

(b) *Combinations of external analgesic active ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics).* (1) The active ingredients of the combination product consist of no more than one single active ingredient from each of the following two groups of analgesic, anesthetic, and antipruritic active ingredients within the concentrations identified in § 348.10(b):
(i) Benzocaine, butamben picrate, dibucaine, dibucaine hydrochloride, dimethisoquin hydrochloride, dyclonine hydrochloride, lidocaine, lidocaine hydrochloride, pramoxine hydrochloride, tetracaine, or tetracaine hydrochloride.
(ii) Benzyl alcohol, camphor, juniper tar, menthol, phenol, resorcinol, phenolate sodium, or thymol.
(2) The active ingredients of the combination product consist of any single active ingredient identified in paragraph (b)(1)(ii) of this section, and any single active ingredient in the following group of analgesic, anesthetic, and antipruritic active ingredients: diphenhydramine hydrochloride, methapyrilene hydrochloride, or tripelennamine hydrochloride.
(3) The active ingredients of the combination product consist of any single active ingredient identified in paragraph (b)(1)(ii) of this section, and camphor and menthol.

(c) *Combinations of external analgesic active ingredients with other externally applied active ingredients.* (1) The active ingredients of the combination product consist of any single active ingredient identified in either paragraph (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this section, and any generally recognized safe and effective skin protectant active ingredient or skin protectant combination of ingredients, provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasion, insect bites, and minor skin irritations, and for the temporary protection and lubrication of minor skin irritations."
(2) The active ingredients of the combination product consist of any single active ingredient identified in either (b)(1)(i), (b)(1)(ii), or (b)(2) of this section, or any combination identified in paragraph (b) of this section, and any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination, provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bits, and minor skin irritations, and for protection against wound contamination."

Subpart C—[Reserved]

Subpart D—Labeling

§ 348.50 Labeling of external analgesic products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s) identified under § 348.10 and identifies the product as follows:
(1) For products containing any external analgesic active ingredients identified in § 348.10 other than hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) identified in § 348.11(b)(10): the labeling identifies the product as an "external analgesic."
(2) For products containing external analgesic products active ingredients identified in § 348.10(b)(10): the labeling identifies the product as an "antipruritic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indication(s)" that is limited to the following phrases:
(1) For products containing any external analgesic active ingredients identified in § 348.10(a): "For the temporary relief of minor aches and pains of muscles and joints, such as simple backache, lumbago, arthritis, neuralgia, strains, bruises, and sprains."
(2) For products containing any external analgesic active ingredients identified in § 348.10(b) other than hydrocortisone preparations (hydrocortisone, hydrocortisone acetate) identified in § 348.10(b)(10): "For the temporary relief of pain and itching due to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations."
(3) For products containing external analgesic active ingredients identified in § 348.10(b)(10): "For the temporary relief of minor skin irritations, itching, and rashes due to eczema, dermatitis, insect bites, poison ivy, poison oak, poison

sumac, soaps, detergents, cosmetics, and jewelry, and for itchy genital and anal areas."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) For products containing any external analgesic active ingredient identified in § 348.10(a) and (b):

(i) "For external use only."

(ii) "Avoid contact with the eyes."

(iii) "If condition worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician."

(iv) "Do not use on children under 2 years of age except under the advice and supervision of a physician."

(2) For products containing any external analgesic active ingredient identified in § 348.10(a):

(i) "Do not apply to wounds or damaged skin."

(ii) "Do not bandage."

(3) For products containing butamben picrate identified in § 348.10(b)(3):

(i) "Do not use over extensive areas of the body."

(ii) "This product stains the skin and tissues, clothing, and other objects yellow."

(4) For products containing any external analgesic active ingredient identified in § 348.10(b)(5), (6), (12), (13), (20), and (21): "Do not use in large quantities, particularly over raw surfaces or blistered areas."

(5) For products containing phenol identified in § 348.10(b) (16): "Do not apply this product to extensive areas of the body or under compresses or bandages."

(6) For products containing resorcinol identified in § 348.10 (b) (18): "Do not apply this product to large areas of the body."

(d) *Directions for use.* The labeling of the product contains the following statement under the heading "Directions": *For adults and children 2 years of age and older:* Apply to affected area not more than 3 to 4 times daily. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a physician.

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before March 6, 1980. Such comments should be addressed to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before April 3, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: November 19, 1979.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 79–36583 Filed 12–3–79; 8:45 am]

BILLING CODE 4110–03–M