to section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that such preparations are safe and effective for the purpose intended.

(d) Any such drug product introduced into interstate commerce that is not in compliance with this section within 30 days after the date of publication of the final order is subject to regulatory action.

2. By adding a new § 700.15 to Subpart B to read as follows:

§ 700.15 Use of certain halogenated salicylanilides as ingredients in cosmetic products.

(a) Halogenated salicylanilides (tribromsalan (TBS, 3,4',5-tribromosalicylanilide), dibromsalans (DBS, 4',5-dibromosalicylanilide, and 3,5-dibromosalicylanilide, and 3,3',4,5'-tetrachlorosayicylanilide (TCSA)) have been used as antimicrobial agents for a variety of purposes in cosmetic products. These halogenated salicylanilides are potent photosensitizers and cross-sensitizers and can cause disabling skin disorders. In some instances the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are deleterious substances which render any cosmetic that contains them injurious to users. Therefore, any cosmetic product that contains such a halogenated salicylanilide as an ingredient at any level for any purpose is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any cosmetic product containing these halogenated salicylanilides as an ingredient that is introduced into interstate commerce 30 days after the date of publication of the final order is subject to regulatory action.

Because of the evidence set forth in the preamble which indicates that these halogenated salicylanilides are not safe for use as active or inactive ingredients in drug and cosmetic products, the Commissioner has determined that it is in the public interest to limit the time for public comment to 30 days.

Interested persons are invited to submit their comments (preferably in quintuplicate) regarding this proposal, on or before October 15, 1974, to the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: August 30, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.74–21054 Filed 9–12–74;8:45 am]

[21 CFR Part 333]

OVER-THE-COUNTER DRUGS

Proposal To Establish a Monograph for OTC Topical Antimicrobial Products

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on July 24, 1974, the report of the Advisory Review Panel on over-the-counter (OTC) antimicrobial drug products for repeated daily human use. In accordance with § 330.10(a)(6), the Commissioner is publishing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC topical antimicrobial drugs are generally recognized as safe and effective and not misbranded, (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel 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 on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above, and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD. 20852.

The Commissioner cautions that the conclusions and recommendations of the Panel must be read and evaluated carefully, to differentiate hypotheses from proven facts. In particular, substantial controversy has already emerged in the course of the Panel deliberations with respect to the hypothesis that the use of antimicrobial agents in bar soaps may selectively kill non-pathogenic gram positive microorganisms resulting in an increase in pathogenic gram negative microorganisms. The Panel has stated, and the Commissioner recognizes, that this hypothesis has not yet been proved by reliable evidence.

The purpose of issuing the unaltered conclusions and recommendations of the Panel, including this hypothesis, is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet evaluated the report, but has concluded that it should first be issued as a formal proposal in order to obtain full public comment before any decision is made on the recommendations of the Panel. The report of this Panel represents their best scientific judgment. It has been prepared independent of the Food and Drug Administration and does not necessarily reflect the Agency's position on any particular matter contained therein. After a careful review of this document and all comments submitted in response to it, the Commissioner will prepare a tentative final regulation to establish a monograph for OTC topical antimicrobial products.

The Commissioner has concluded that, to assure implementation of the Panel's recommendations, both cosmetic as well as drug regulations should be promulgated. The present Federal Food, Drug, and Cosmetic Act provides no legal authority under which the Agency can reclassify cosmetics as drugs, but does permit regulation of cosmetic ingredients. It is the Commissioner's intent to propose regulations under sections 601(a) and 602(a) of the act to apply the same safety and labeling standards to cosmetics containing antimicrobial ingredients subject to this notice as are applied to OTC drug products containing these ingredients.

It is also the Commissioner's intent to promulgate regulations in the Tentative Final Monograph to distinguish between preservative and active levels of antimicrobials. While the Commissioner takes no position at this time on the preservative test recommended in the Panel report, it is his intent to require either a preservative test or specific maximum preservative levels for antimicrobial ingredients in OTC drug products and cosmetics.

In accordance with § 330.10(a)(2), all data and information concerning OTC antimicrobial drug products for repeated daily human use submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration on or before October 15, 1974, 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 shall be submitted to the Food and Drug Administration, Bureau of Drugs, OTC Drug Products Evaluation Staff (HFD–109), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the monograph (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 on the basis of the Panel determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (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 whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 1 year after the date of publication of the final monograph

in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The conclusions and recommendations contained in the report of the Advisory Review Panel on Over-The-Counter (OTC) antimicrobial drug products for repeated daily use to the Commissioner are as follows:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. The Commissioner issued in the FEDERAL REGISTER of January 7, 1972 (37 FR 235) a request for data and information on all antimicrobial active ingredients in drug products for repeated daily topical human use. A clarifying call for data and information was published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775).

On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 (formerly § 130.301) published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC products containing antimicrobial ingredients for topical human use, which includes soaps, surgical scrubs, skin washes, skin cleansers and first-aid preparations, pursuant to § 330.10(a)(1).

Harvey Blank, M.D., Chairman; Frank B. Engley, Jr., Ph.D.; William L. Epstein, M.D.; Wallace L. Guess, Ph.D.; Florence K. Kinoshita, Ph.D. (resigned from the Panel in September, 1973); Mary Marples, M.A., M.D., D.T.M. and H. (resigned from the Panel in January, 1974); Paul D. Stolley, M.D.

The Panel was convened first on June 29, 1972, in an organizational meeting. Fifteen working meetings were held on August 16, 17, and 18; September 14, 15, and 16; October 19, 20, and 21; November 18, 19, and 20; December 14, 15, and 16, 1972; February 8, 9, and 10; March 3, 4, and 5; April 25, 26, and 27; June 7, 8, and 9; July 7, 8, and 9; August 30, 31, and September 1; September 27, 28, and 29; November 29 and 30, 1973; February 3, 4, and 5; and June 1 and 2, 1974.

Three non-voting liaison representatives, Ms. Sarah Newman nominated by an ad hoc group of consumer organizations; Joseph M. Pisani, M.D., nominated by the Proprietary Association; and Robert Giovacchini, Ph.D., nominated by the Cosmetic, Toiletry and Fragrance Association, participated in Panel discussions. Food and Drug Administration employees included Ms. Mary Bruch who served as Executive Secretary, Michael Kennedy as Panel Administrator, and Melvin Lessing, M.S., R.Ph. as Drug Information Analyst.

In addition to the Panel members and liaison representatives, the Panel utilized the advice of one consultant, Richard Marples, B.M., M.Sc.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

Richard Baughman, M.D.; Abe Cantor, Ph.D.; Salvatore De Salva, Ph.D.; Hans P. Drobeck, Ph.D.; Mr. T. E. Furia; Sol Gershon, Ph.D.; Donovan E. Gordon, D.V.M., Ph.D.; Alfred Halpern, Ph.D.; Gavin Hildick-Smith, M.D.; Ira Hill, Ph.D.; John Kooistra, Ph.D.; Frank Lyman, M.D.; Milton Manowitz, Ph.D.; Ben Marr-Lanman, M.D.; Mr. Nicholas Molnar; Joseph Page, Esq.; Gerald Rice, M.D.; Dan Roman, Ph.D.; Louis Scharpf, Ph.D.; Edward Singer, Ph.D.; Richard Sykes, Ph.D.; David Taber, Ph.D.; Mr. David Taplin; Monroe Trout, M.D.; Leonard Vinson, Ph.D.; Mr. Anthony Young.

No other person requested an opportunity to appear before the Panel.

SUBMISSION OF DATA AND INFORMATION

Pursuant to the notices published in the FEDERAL REGISTER of January 7, 1972 (37 FR 235) and April 4, 1972 (37 FR 6775) requesting the submission of data and information on antimicrobial ingredients in OTC drugs, the following firms made submissions relating to marketed products:

Firm	*Marketed Products*
Alexander Manufacturing Co., Texarkana, Ark. 75501.	Alexander's Dand-Ex.
Apple-Crone Drugs Laboratories, Southfield, Mich. 48075.	Apple-Crone Hair and Scalp Conditioner.
Armour-Dial, Inc., Chicago, Ill. 60608	Dial Soap.
Ayerst Laboratories, New York, N.Y. 10017	Dermoplast Aerosol.
Bowman Pharmaceuticals, Inc., Canton, Ohio 44702.	Surgical Soap with 2 percent hexachlorophene.
Calhoun's Laboratory, Savannah, Ga. 31405	Dyper-Rash-Eze and Fung-O Ointment.
Campana Corp., Batavia, Ill. 60510	Cuticura Medicated Soap.
C. R. Canfield & Co., Minneapolis, Minn. 55408.	Sebacide.
Chase Chemical Co., Cleveland, Ohio 44110	Donovo and Glov-Kote.
Chesebrough-Pond's, Inc., Clinton, Conn. 06413.	Vaseline First Aid. Carbolated Petrolatum Jelly and Virac Topical Germicide.
Ciba-Geigy Corp., Ardsley, N.Y. 10502	Irgasan® DP-300 (Triclosan), Irgason® CF 3 (Cloflucarban).
Colgate-Palmolive Co., New York, N.Y. 10022	Dermassage Lotion, P-300 Soap Bar, Tackle Gel, Washkins, Wash'n Dri, and Wash'n Dri Washkins for Babies.
Eby Chemical Co., Harrisburg, Pa. 17105	Ecco Medicated Powder.
Factor, Max and Co., Hollywood, Calif. 90028	SEBB Lotion.
The Falk Co., Wayzata, Minn. 55391	Falk's Camfo Creme.
Ferro Corp., Toledo, Ohio 43605	Ottasept.
Fine Organics, Inc., Lodi, N.J. 07644	Temasept IV (Tribromsalan).
Gaby, Inc., Philadelphia, Pa. 19125	Gaby Greaseless Suntan Lotion and G-63.
T. R. Gibbs Medicine Co., Inc., Washington, D.C. 20020.	T. R. Solution.
Givaudan Corp., Clifton, N.J. 07014	G-11 (Hexachlorophene).
Goyescas Corp. of Florida, Miami, Fla. 33142.	Princeladas Goyescas.
Gypsy Remedy Co., Ocala, Fla. 32670	Gypsy's Wonder Ointment.
Harrison's Laboratories, Jackson, Miss. 39201	Harrison's Lotion.
Herald Pharmacal, Inc., Bedford, Va. 24523	H. A. F. Ansel Antiseborrheic Lotion and Seborid Shampoo.
High Chemical Co., Philadelphia, Pa. 19122	Klorlyptus Oil and Klorlyptus Ointment.
Huntington Laboratories, Inc., Huntington, Ind. 46750.	G.S.I. Iodine Surgical Detergent and Sana-Prep Pre-Surgical Preparation.
Indiana Botanic Gardens, Hammond, Ind. 46325.	Vanishing Balm.
The Jola Co., Milwaukee, Wis. 53210	"Jola" Xeem Cream.
F. N. Kalert Co., St. Louis, Mo. 63125	Formula 59 Foot Soap.
King Laboratories, Richardson, Tex. 75080	Pedolatum.
Laboratory Robaina, Inc., Hialeah, Fla. 33010	Acetolia Robaina and Jabon Acetolia.
Lam Enterprises, Honolulu, Hawaii 96817	Liquid Taizema, Green Remedy, Taizema Ointment, and Zenji Sui.
Larson Laboratories, Inc., Erie, Pa. 16505	Foot Note.
Legulo Pharmaceutical Mfr., Chicago, Ill. 60634.	Legulo and Legulo, Mild.
Lyne Laboratories, Winchester, Mass. 01890	Hexa-Cet.
Macsil Inc., Philadelphia, Pa. 19125	Balmex Medicated Lotion.
Marika of Albuquerque, Albuquerque, N.M. 87106.	Verdi Lotion.
Mecos, Inc., New Orleans, La. 70113	Wylon Scalp Treatment.
Merck, Sharp and Dohme Research Laboratories, West Point, Pa. 19486.	Approve, F.P.S. Skin Cleaner, and S.T. 37 Antiseptic Solution.
Meri Jo Inc., Tampa, Fla. 33614	Fine Fungicide and Korn Kure.
Miles Laboratories, Inc., Elkhardt, Ind. 46514	Bactine, Bactine Aerosol, and Bactine Towelettes.
Mon-Ray Chemical Co., Forest City, N.C. 28043.	Mon-Ray Formula 222.

Firm	*Marketed Products*
Monsanto Industrial Chemicals Co., St. Louis, Mo. 63166.	Triclocarban.
Nitine, Inc., Clifton, N.J. 07015	Nitex.
Norwich Pharmacal Co., Norwich, N.Y. 13815	Unguentine Aerosol, Unguentine Original Formula, Unguentine Plus, and Unguentine Spray.
Oxford Chemicals, Atlanta, Ga. 30341	Garvoderma, Oxford Phex, Oxford Pro-Med, Oxford Pro-Med (odorless), Oxford San-O-Sep, and Oxford Sep.
Parke, Davis and Co., Detroit, Mich. 48232	Liquid Germicidal Detergent, Phemerol Solution, Phemerol Tincture, and Phemerol Topical.
Pfister Chemical Inc., Ridgefield, N.J. 07657	TBS-100 (Tribromsalan).
Phenex Antiseptic Laboratories, Inc., Chicago, Ill. 60641.	Phenex Antiseptic, Phenex Ointment 30%, and Phenex Skin Lotion.
Plough, Inc., Memphis, Tenn. 38101	Clean 'N Treat, Mexsana Medicated Powder, Solarcaine Cream, Solarcaine Foam, Solarcaine Lotion, and Solarcaine Spray.
Wm. P. Poythress and Co., Inc., Richmond, Va. 23217.	Bensulfoid Lotion.
The Procter and Gamble Co., Cincinnati Ohio 45217.	Safeguard Soap.
The Purdue Frederick Co., Yonkers, N.Y. 10701.	Betadine Aerosol Spray, Betadine Ointment, Betadine Skin Cleanser, Betadine Solution, Betadine Surgical Scrub, and Betadine Surgical Scrub/Skin Cleanser.
Red Foot Products Co., Inc., Detroit, Mich. 48228.	Redfoot Corn and Callus Remover, and Redfoot Powder.
Resinol Chemical Co., Baltimore, Md. 21201	Resinol Greaseless Cream and Resinol Ointment.
The Rllox Co., New Orleans, La. 70122	Geneva Ointment and Shave Losh.
Rystan Company, Inc., Little Falls, N.J. 07424.	Prophyllin Ointment and Prophyllin Powder.
Savoy Drug and Chemical Co., Michigan City, Ind. 46360.	Special Ointment and Special Foot Powder.
R. Schattner Co., Washington, D.C. 20016	Oraderm Lip Lotion and Chloraderm.
Sherwin Williams Chemicals, Toledo, Ohio 43608.	Tribromosalicylanilide.
Smith, Kline and French Laboratories, Philadelphia, Pa. 19101.	Acnomel Cake, Acnomel Cream, and Pragmatar.
Sterling Drug Inc., New York, N.Y. 10016	Campho-Phenique Liquid, Campho-Phenique Powder, Fisohex, Hexachlorophene, Medi-Quik, PhisoHex, Phiso-Scrub, Roccal, Sarene, Soapure, Zephiran Aqueous, Zephiran Chloride, Zephiran Chloride Tincture, Zephiran Spray, Zephiran Towelettes, Zobenol Aqueous, and Zobenol Tincture.
United States Borax and Chemical Corp., Los Angeles, Calif. 90010.	Luron Lotion Soap, MD*7 Lotion Soap, and Tomac Lotion Soap.
The Upjohn Co., Kalamazoo, Mich. 49001	Mercresin Tincture.
R. T. Vanderbilt Company, Inc., New York, N.Y. 10017.	Vancide 89RE and Vancide FP.
Vestal Laboratories, St. Louis, Mo. 63110	Septisol.
Wade Chemical Corp., Shreveport, La. 71103	Jim Wade Foot Medicine.
West Chemical Products, Inc., Long Island City, N.Y. 11101.	Ionol, Prepodyne Scrub, Prepodyne Solution, Prepodyne Concentrate, Tamed-Iodine Scrub, and Wescodyne.
Woolley Chemical Co., Ogden, Utah 84401	Treu-Youth Hand Balm and Treu-Youth Lotion Pack.

In addition, the following firms made related submissions:

Firm	*Submissions*
Armour-Dial, Inc., Chicago, Ill. 60608	Hexachlorophene, Tribromsalan, and Triclocarban.
Lever Brothers Co., Edgewater, N.J. 07020	Tribromsalan.
Millmaster Onyx Corp., Jersey City, N.J. 07302.	Quaternary Ammonium Salts.
The Procter and Gamble Co., Cincinnati, Ohio 45217.	Cloflucarban, Hexachlorophene, Tribromsalan, and Triclocarban.
The Purdue Frederick Co., Yonkers, N.Y. 10701	Iodophors.
Sterling Drug Inc., New York, N.Y. 10016	Benzalkonium Chloride, Methylbenbethonium Chloride, and Tribromosalicylanilide.
West Chemical Products Inc., Long Island City, N.Y. 11101.	Iodophors.

The labeled ingredients contained in these products are as follows:

Acetone
Alkyl amine of lanolic acids
Allantoin
Alrosol
Aluminum hydroxide
Aluminum potassium sulfate
Ammonia solution
Balsam Peru
Bentonite
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Benzoin fluidextract
Benzyl alcohol
Bismuth subcarbonate
Bismuth subnitrate
Boric acid
Boric acid glycerite
Butylated hydroxytoluene
Calamine
Camphor
Captan (N-trichloro-methylthio-4-cyclohexene-1, 2-dicarboximide)
Castor oil
Cetyl alcohol
Cetyl alcohol-coal tar distillate
Chlorobutanol
Chlorophyll
Chlorothymol
Citric acid
Cloflucarban
Coal tar, crude
Coconut oil
Collodion
Cornstarch
Dipropylene glycol
Dodecylbenzene sulfonate
Entsufon
Ether
Eucalyptol
Eucalyptus dichloride
Eucalyptus oil
Eugenol
Ferric chloride
Fluorosalan
Glycerin
Goose grease
Hexylresorcinol
Hexachlorophene
8-Hydroxyquinoline benzoate
Iodine complexed with phosphate ester of alkylaryl polyethylene glycol
Juniper tar
Kaolin
Lanolin
Lanolin, anhydrous
Lanolin, cholesterols
Lanolin, modified, ethoxylated
Lanolin, hydrous
Lecithin
Lidocaine hydrochloride
Magnesium stearate
Menthol
Mercuric chloride
Methylbenzethonium chloride
Methylcellulose
Methylparaben
Methyl salicylate
Mineral oil, refined
Nonylphenoxypolyethoxyethanol
Nonylphenoxypoly-(ethyleneoxy) ethanoliodine complex
Oleostearin
Orthochloromercuriphenol
Orthohydroxy phenylmercuric chloride
Oxyquinoline sulfate
Para-chloro-meta-xylenol
Parahydrecin
Petrolatum
Phenol
Phenyl salicylate
Pine oil
Pine tar
Poloxamer-iodine complex
Polyoxyethylene lauryl ether
Polysorbate
Polysorbate 20
Potassium alum
Potassium coconut soap
Potassium salt of cocoyl - polypeptide condensate
Povidone-iodine complex
Propylene glycol
Propionic acid
Propylparaben
Quaternary ammonium compounds
Quince seed mucilage
Resorcinol
Resorcinol monoacetate
Rosin
Salicylic acid
Saponified greases
Secondary - amyltricresols
Sequestrene 50 K3
Silicone
Sodium biphosphate
Sodium borate
Sodium citrate
Sodium phenolate (phenate)
Sodium propionate
Sodium salicylate
Sodium salicylic acid phenolate
Sodium undecylenate
Storax
Sucrose octaacetate
Sulfur

Sulfur, colloidal
Sulfur, flowers of
Sulfur, precipitated
Tannic acid powder
Tetracaine hydrochloride
Thymol
Tragacanth
Tribromsalan
Triclocarban
triclosan
Triethanolamine
Triton X-100
Undecoylium chloride-iodine
Undecylenic acid
White oil of thyme
Zinc acetate
Zinc carbonate
Zinc oxide

CLASSIFICATION OF INGREDIENTS

The Panel has classified the following ingredients into groups identified below:

ANTIMICROBIAL INGREDIENTS

Quaternary ammonium compounds:
- Benzalkonium chloride
- Benzethonium chloride
- Methylbenzethonium chloride

Cloflucarban
Fluorosalan
Hexachlorophene
Hexylresorcinol
Iodophors:
- Nonylphenoxypoly (ethyleneoxy) ethanol—iodine complex
- Poloxamer—iodine complex
- Povidone—iodine complex
- Iodine complexed with phosphate ester of alkylaryl polyethylene glycol
- Undecoylium chloride—iodine complex

Para-chloro-meta-xylenol
Phenol(s):
- Secondary-amyltricresols
- Sodium phenolate

Tincture of iodine
Tribromsalan
Triclocarban
Triclosan
Triple dye (see discussion elsewhere in the document).

ANTIMICROBIAL INGREDIENTS COMBINED WITH NON-ANTIMICROBIAL ACTIVE INGREDIENTS

If a product contains an antimicrobial ingredient and meets the definitions adopted by the Panel, it may be combined with other non-antimicrobial active ingredient(s): *Provided,*

(1) The antimicrobial ingredient remains safe and effective;

(2) The non-antimicrobial active ingredient is safe and effective;

(3) The labeling indicates the pharmacologic effects of all active ingredients;

(4) The combination provides rational concurrent therapy for a significant portion of the target population;

(5) The combination meets the requirement of the definitions for the antimicrobial product categories.

The Panel is particularly concerned that the combination not delay wound healing. If a skin antiseptic claim is made it must meet the requirement of the definition of a skin antiseptic described elsewhere in this document.

INGREDIENTS DEFERRED TO ANTIMICROBIAL II PANEL

Antimicrobial ingredients formulated in products labeled for use for specific indications, such as dandruff and seborrhea, acne, athlete's foot, and otitis externa will be included in the second part of the Panel's review, Antimicrobial II.

Captan
Coal tar, crude
Juniper tar
Pine tar
Propionic acid
Resorcinol
Resorcinol monoacetate
Salicylic acid
Salol—phenyl salicylate
Sodium undecylenate
Storax
Sulfur, colloidal
Sulfur, flowers of
Sulfur, precipitated
Tannic acid
Thymol
Undecylenic acid
*White oil of thyme

INGREDIENTS DEFERRED TO OTHER PANELS

Data for several ingredients, frequently formulated with antimicrobials, were also submitted.

The following ingredients are all topical analgesics and have been deferred for review to the Topical Analgesic Panel:

Benzocaine
Camphor (refer to statements for phenol)
Lidocaine hydrochloride
Menthol
Methyl salicylate
Tetracaine hydrochloride

The following ingredients are all mercurials and have been deferred for review to the Miscellaneous Topical Panel:

Mercuric chloride
Orthochloromercuriphenol
Orthohydroxyphenylmercuric chloride

PRESERVATIVE LEVELS OF ACTIVE INGREDIENTS

The active antimicrobial ingredients reviewed by the Panel can be formulated in topical products at various concentrations. The minimum concentration required for effectiveness as an active ingredient will be established by in vitro and in vivo efficacy testing as will the range of concentrations which can be safely used. The Panel recognizes that many of these antimicrobial ingredients might also be added to products at much lower levels to prevent the spoilage of products and to protect them from the growth of microorganisms introduced as a result of customer use. Many of the antimicrobials reviewed are primarily active against gram positive microorganisms and would not generally be considered as good candidates for use as preservatives. However, some of these may be considered for use as part of a preservative system.

If an antimicrobial ingredient is to be used as a preservative, evidence should be available to demonstrate that the concentration used is the minimum at which it is effective as a preservative. The procedure for establishing the minimum effective preservative concentration(s) is the United States Pharmacopeia (USP), "Antimicrobial Agents—Effectiveness Test" under Microbiological Tests (currently, USP XVIII, p. 845). The safety should also be established according to the statements on individual ingredients and the Guidelines in this document.

Considerations other than antimicrobial activity are important in the selection of a preservative and usually include: Activity at low concentrations, solubilities and partition coefficients in the various types of formulations in which they are used.

Based on the data presently available, Category II ingredients which are Category II for all product categories (see discussion elsewhere in this document) are not recommended for use as preservatives under any circumstances.

The question of the adequacy of the following ingredients as preservatives will not be discussed at this time but will be considered by the OTC Antimicrobial II Panel.

Benzoic acid
Benzyl alcohol
Boric acid
Chlorobutanol
Chlorothymol
8-Hydroxyquinoline benzoate
Methylparaben
Oxyquinoline sulfate
Propylparaben
Sodium propionate

One manufacturer submitted data claiming oxyquinoline sulfate as an active ingredient in a formulated product (Ref. 1). The Panel has classified this ingredient as a preservative, similar to those submitted in other formulations. As has been stated, the concentration of the antimicrobial and time of exposure, among other parameters, determines the clinical effectiveness of an antimicrobial.

The claim submitted for oxyquinoline sulfate at a 0.03 percent level is based entirely on in vitro data. The agar-well technique to determine zones of inhibition was used. The tests were conducted with 0.03 percent oxyquinoline sulfate plus other preservatives (methylparaben and propylparaben). Zones of inhibition were determined for the formulation but not for individual ingredients.

Methylparaben, propylparaben and oxyquinoline sulfate are listed as active ingredients in the formulation at levels currently used in many lotion formulations as preservatives to maintain the quality of the lotion and prevent microbial contamination with use. No in vivo studies were submitted to support the effectiveness of oxyquinoline sulfate as a clinically active ingredient on the skin. Therefore, the Panel has classified the ingredient as a product preservative.

REFERENCES

(1) OTV Volume 020054.[1]

INACTIVE INGREDIENTS

Inactive ingredients are useful in the manufacturing of pharmaceutical preparations to enhance the quality and/or appearance of the product. This list reflects only those inactive ingredients contained in the labeled ingredients submit-

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER. The volumes are on file in the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

ted to the Panel and is not intended to be an exhaustive list.

Acetone
Alkyl amine of lanolic acids
Allantoin
Alrosol
Aluminum hydroxide
Aluminum potassium sulfate
Ammonia solution
Balsam Peru
Bentonite
Benzoin fluid extract
Bismuth subnitrate
Bismuth subcarbonate
Boric acid glycerite
Butylated hydroxytoluene
Calamine
Castor oil
Cetyl alcohol
Chlorophyll
Citric acid
Coconut oil
Collodion
Cornstarch
Dipropylene glycol
Dodecylbenzene sulfonate
Entsufon
Ether
Eucalyptol
Eucalyptus dichloride
Eucalyptus oil
Eugenol
Ferric chloride
Glycerin
Goose grease
Kaolin
Lanolin
Lanolin, anhydrous
Lanolin, chlolesterols
Lanolin, modified ethoxylated
Lanolin, hydrous
Lecithin
Magnesium stearate
Methylcellulose
Mineral oil, refined
Nonylphenoxypoly-ethoxyethanol
Oleostearin
Parahydrecin
Petrolatum
Pine oil
Polyoxyethylene lauryl ether
Polysorbate
Polysorbate 20
Potassium alum
Potassium coconut soap
Potassium salt of cocoyl—polypeptide condensate
Propylene glycol
Quince seed mucilage
Rosin
Saponified greases
Sequestrene 50 K3
Silicone
Sodium biphosphate
Sodium borate
Sodium citrate
Sodium salicylate
Sodium salicylic acid phenolate
Sucrose octaacetate
Tragacanth
Triethanolamine
Triton X–100
Zinc acetate
Zinc carbonate
Zinc oxide

The OTC Antimicrobial I Panel was charged with the review and evaluation of safety and effectiveness data on antimicrobial ingredients and combinations in topically applied OTC products.

An outline was developed by the Panel to evaluate the data from all the submissions for ingredients (Ref. 1). The outline was made at the beginning of the Panel's deliberations to provide a checklist for the information in the data submissions supplied to the Panel. During its deliberations, other modified guidelines for the evaluation of antimicrobial ingredients were developed and are included in this document.

The report of this Panel deals with antimicrobial ingredients in the following products: Soaps, surgical scrubs, skin washes, skin cleansers, first-aid preparations, and additional products defined by the Panel.

The Panel defined an "antimicrobial ingredient" as an agent which kills or inhibits the growth and reproduction of micro-organisms. Many products formulated with antimicrobials for use as handwashing products, surgical scrubs or so-called "antiseptics" are marketed as concentrates with label directions for dilution prior to use. The dilution recommended for use, as distinguished from the marketed concentrates, is defined in this report as the "use concentration" or the "use dilution." The Panel in its deliberations considered the activity of these ingredients at "use concentrations".

The Panel recognized that many ingredients reduce the number of microorganisms on the skin. The normal flora of micro-organisms on the skin has been divided traditionally into "transient" and "resident" flora (Ref. 2). The transient flora can be considered the organisms which are picked up from contact with the environment or from other persons and which are not part of the established normal flora. These organisms are easily removed from the upper layer of the skin along with dirt particles and oil. However, a transient organism may become part of the resident established flora. In contrast, the resident flora is usually considered the organisms which constitute the established flora of the skin.

The ingredients reviewed by the Panel are formulated in products designed to reduce microbial flora on the skin. The intended effect ranges from the reduction of acquired pathogens on the skin to the reduction of the normal resident flora to low levels. Some products are used on the skin with more than one intended effect. There has been widespread use of antimicrobials in soap, surgical scrubs and pre-operative preparations based on the view that the reduction of normal flora to as low a level as possible will have a positive effect on the prophylaxis of disease. The interrelationship of the concentration, time of action or contact time, the microbial spectrum, and the possible deleterious effect of drastic changes in the normal skin flora have been largely ignored in the past or only superficially investigated. The Panel concludes the interrelation of findings of this type to the mitigation, treatment or prevention of infection has not been established by the data submitted.

Since topical products without an active ingredient frequently have a substantial effect, there should be some demonstration that the formulated product with the active ingredient is better than the vehicle alone. In the case where a test of effectiveness is performed, the vehicle should be used as a control. Emollient effect is obvious with the vehicle of many topical products. For instance, the contribution of this effect to wound healing, or its relationship to the effectiveness of an antimicrobial product is unknown.

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1. *Effectiveness of antimicrobial bar soap—Balance of normal skin flora.* It is well recognized that the human skin carries a population of micro-organisms known as the normal flora. The numbers vary among individuals and in different locations on the same individual. The predominant members of the normal flora are gram-positive cocci and diphtheroids. These groups are not only regarded as harmless on the intact skin but are considered to have a protective effect against potential pathogenic microorganisms. Small numbers of gram negative species, such as the coliforms and related organisms, as well as higher forms, such as yeasts may be residents of the skin of healthy individuals. In certain circumstances, where the composition of the gram positive micro-organisms are altered, dense populations of gram negative micro-organisms may develop.

It has been demonstrated by Ehrenkranz et al. (Ref. 1) that with continued washing of the feet twice a day for 2 weeks, a *Pseudomonas* colonization was established on the foot washed with antibacterial soap (containing triclocarban, tribromsalan and cloflucarban) and not on the (control) soap-washed foot. This work has been confirmed with a larger group of subjects by Amonette and Rosenberg (Ref. 2) by Taplin (Ref. 28) and by Marples (Ref. 3). With other antimicrobials, Taplin (Ref. 4) has reported to the Panel that their use removes some protective advantages of the gram positive flora, especially against colonization with *Pseudomonas*. These studies demonstrate the potential harmful shift in the normal flora of the skin which may occur with the repeated use of gram-positive bacteriostatic products. Marples has shown the enormous increase in the resident microflora occurring when the skin is covered with an impermeable film as well as the influence of gram-positive bacteriostats in this test system which can result in the occurrence of a high gram-negative population on the skin (Ref. 29 and 30). Reports that changes in the normal flora of the hands occurred after the use of products containing gram-positive bacteriostats and resulted in carriage of gram negative organisms have been made by Bruun and Solberg (Ref. 31) and by Brown (Ref. 32). A protective function of resistance to certain infections has been postulated for the normal flora, particularly the diphtheroid population of the skin by Marples (Ref. 3, 4 and 28).

The Panel states their concern to that already widely expressed in the scientific community that the widespread use of anti-gram-positive antibiotics, antimicrobials on the skin, and hard surface disinfectant products which are frequently active only against gram positive organisms has produced a tremendous increase in gram negative infections in hospitals and other closed environments (Ref. 33). The Panel recognizes that the isolation of any one factor as responsible for cause and effect is difficult. However, they believe that there is sufficient evidence to postulate an effect from the use of topical antimicrobials.

Deodorant effect. The reduction of the normal skin flora, particularly the gram positive flora, has a deodorant effect. Dravnieks et al. (Ref. 5), Meyer-Rohn (Ref. 6), Shehadeh and Kligman (Ref. 7) and Shelley et al. (Ref. 8) have established the relationship of the gram positive flora to odor. It was the estimate of a group of experts from industry and academia (who appeared before the Panel to discuss the effectiveness of antimicrobials in the classes of products currently being reviewed by the Panel) that approximately a "70 percent reduction" in the microbial flora (as measured by hand-washing tests) would produce a deodorant effect. The exact percent reduction required to achieve a deodorant effect either on the entire body or in the axillae was not established by the data submitted. The view of the Panel is that perhaps some bar soaps which achieve a 90 percent or more reduction of gram positive organisms may be so active as to be harmful (Refs. 1 through 4).

The concentration of any antimicrobial incorporated into a bar soap should be set at a level which reduces the microbial flora sufficiently to produce a deodorant effect. Currently, neither the amount of the antimicrobial needed nor the degree of reduction of the hand flora (measured in handwashing tests) needed to achieve this can be stated conclusively. The Panel hopes that these uncertainties can be resolved with increasing refinement of effectiveness tests and expansion of effectiveness testing to include areas of the body other than the hands.

Classical ecological studies have shown only too clearly the dangers of altering a stable community of any type, including microorganisms (Marples, Ref. 9; Rosebury, Ref. 10). While a reduction of the cutaneous population of gram positive microorganisms does have a deodorant effect, such a change may be disadvantageous to the host, since not only is there no conclusive evidence that the antimicrobial reduces or prevents infection, but its action may even enhance the growth of a potentially pathogenic microorganism.

Data are accumulating which indicate that shifts and/or alteration in the composition of the normal skin flora are harmful (Refs. 1, 2, 3, 29, 31 and 32). It is the judgment of the Panel that until definitive data are available it is prudent to avoid significant alterations in the normal flora. These shifts or alterations in normal flora may even be more hazardous in an institutional setting (closed population) or with individuals who have altered susceptibilities.

Wound healing. In animal models the use of certain antimicrobials in liquid soap retarded wound healing. Dajani et al. (Ref. 11) and Custer et al. (Ref. 12) showed retardation of healing in artificially contaminated animal wounds treated with polyvinyl pyrrolidone-iodine complex and 3 percent hexachlorophene. Edlich et al. (Ref. 13) indicate that the ratio of ethylene oxide to propylene oxide in the block polymers (pluronic polyols) determines the tissue toxicity of surfactants used alone or complexed with iodine (for further details refer to comment on Iodophors). Data with respect to wound healing with bar soaps were not submitted. In a recent study in humans by Ruby and Nelson (Ref. 14), however, scrubbing the lesions of impetigo with a hexachlorophene soap had no appreciable beneficial or adverse effect on wound healing.

Prevention of skin infections. Attempts have been made to demonstrate clinical effectiveness in the prevention of minor skin infections with the use of soaps containing an antimicrobial.

Three studies, performed at the military service academies, were designed and executed in the attempt to show that prophylaxis of minor skin infections can be achieved with the use of an antimicrobial bar soap. There were variations in the control of the subjects, the extent of laboratory analysis of cultures, and the critical character of the diagnosis of lesions and followup of the subjects. Essentially, the overall design was similar. Certain companies of men were assigned to "test soap" and others to "control soap".

The collective description of cutaneous infection or cutaneous pyodermas is divided into specifically defined clinical entities in the discussion of the results of these studies. The terms used to define specific skin infections are furuncles, furunculosis, or multiple furunculosis, paronychia, pustular folliculitis, impetigo, and secondarily infected abrasions and blisters. These are all commonly used medical terms.

In all cases attempts were made to eliminate the concomitant use of other drug and cosmetic products containing an antimicrobial.

Chronologically, the first was a 2 month study performed by Leonard at West Point in 1966. The test soap bar contained a 2 percent mixture of three antimicrobial ingredients: Tribromsalan, triclocarban, and cloflucarban. The author's summary (Ref. 15) indicates a 44 percent reduction in superficial cutaneous infections.

When a direct comparison of total incidence of cutaneous infections is made, there appears to be a significant difference. The incidence of single furuncles was significantly higher in the control group. However, if only the incidence of multiple furunculosis is examined, the difference is not significant. Also, there were more paronychial infections among the men using the antibacterial soap bar than among those using the control bar.

Dr. Clarence Livingood (Ref. 16), who has closely checked the results of the three studies, has communicated his view that the analysis of the results in all three studies are equivocal and may be explained, in part, as follows:

(1) There was variation in diagnosis resulting from the use of more than one physician for diagnosis.

(2) It seemed probable that a 2 month study was too short to establish the expected results.

(3) The results of the bacteriologic cultures were not included.

(4) The initial infection rate was not uniform in the test groups.

At about the same time as the West Point Study, MacKenzie (Ref. 17) conducted a 6 month study at the Naval Academy at Annapolis with a soap containing 0.75 percent triclocarban and 0.75 percent hexachlorophene. The effect of soap usage on different types of lesions was described in the report of the study. The incidence of both furunculosis and secondarily infected skin lacerations was also the same in the control and treated groups. However, there was a lower incidence of cellulitis secondary to trauma and pustular folliculitis in the test group using antibacterial soap.

The results of another but unpublished study at Annapolis were also commented on by Dr. Livingood. In this case, a soap containing 2 percent mixture of tribromsalan, triclocarban, and cloflucarban, different from that used in the first Annapolis study, was tested. The results showed no reduction in furunculosis or paronychia in the groups using the antimicrobial soap. Again, there was a reduction in infections as complications of minor traumatic injuries.

It is the Panel's view that conclusions cannot be drawn with respect to the prophylaxis of cutaneous skin infections from a comparison of the specific lesions which occurred in both groups.

In 1969 Duncan et al. (Ref. 18) compared inhabitants of two Texas prison farms, one of which used an antimicrobial soap bar (2 percent mixture of tribromsalan, cloflucarban, and triclocarban) while the other did not. This study, monitored by the Armed Forces Epidemiology Board, was performed in an attempt to resolve the persistent questions of effectiveness raised by the two earlier published studies. Again, unequivocal conclusions could not be drawn from data presented comparing the incidence of skin infection in the treated and control groups.

A study was performed in a home for the mentally retarded in Ellisville, Mississippi by Wheatley et al. (Ref. 19). The authors reported that the use of an antimicrobial soap bar significantly reduced the incidence of superficial cutaneous pyogenic infections. A careful review of this unpublished paper by the Panel and by a statistician led to the conclusion that the interpretation of the data by the authors could not be accepted due to problems of study design and analysis.

The most important difficulty encountered was the assumption that the "observations" were independent (an observation was the weekly infection rates). Inappropriate statistical tests of significance were applied. The basic outcome measure (weekly infection rates) was called into question and the raw data were requested so that the study could be re-analyzed. The company sponsoring the study was unable to supply these data and it was felt that no inferences as to effectiveness could be drawn from the data presented in the report that was submitted to the Panel.

Studies among combatants in Vietnam and also among military personnel and children in Colombia, South America performed by Allen and Taplin et al. (Ref. 20 and 21) suggested that the use

of an antimicrobial soap did not prevent infection under stress conditions. And in fact, streptococcal skin infection continued to be the most common cause of disability from superficial infections among the troops. These studies also indicated that hygiene and climate are important determinants in the development of superficial staphylococcal and streptococcal infections.

The Panel reviewed the clinical studies designed to show effectiveness in the prevention of minor skin infections. These studies were found insufficient to support a conclusion of effectiveness.

Acute glomerulonephritis is one of the more serious complications which may follow streptococcal skin infection. Nephritis may also follow streptococcal throat infections. No all strains of *Streptococcus* are nephritogenic. The streptococcal types associated with nephritis following impetigo or pyoderma are not the same ones associated with nephritis following streptococcal pharyngitis (Ref. 22). The risk of nephritis following a streptococcal skin infection with a nephritogenic strain is about 12 percent (Ref. 23). This relationship has also been described by Dillon et al. (Ref. 24), Department of the Army (Ref. 25) and Kelly and Taplin (Ref. 26). Allen and Taplin (Ref. 20), Taplin et al. (Ref. 21) and Dillon (Ref. 27) have shown the high incidence of streptococcal sores in indigent children and in children in tropical climates. In addition, the Panel's concern is also based in part on the great increase in all types of gram negative infections, including *Pseudomonas* infections, in hospitals where anti-gram positive agents are in wide use (Ref. 33).

Because of the information called to the Panel's attention they have been concerned that routine use of antimicrobial soaps may have a long-term harmful effect by reducing the protective effect of the normal skin flora. It is possible that contrary to what might be expected from an antibacterial product that certain bacterial infections due to gram-negative and streptococcal organisms might be increased, rather than decreased. If this is proven to be true, the deodorant benefit would probably be considered outweighed by the potential hazard. In addition, because these chemicals are absorbed into the bloodstream, the Panel is concerned about the prudence of exposing the entire body surface to these chemicals when alternative methods of odor control are available.

The Panel has been particularly concerned that some soap and detergent bars containing antimicrobial ingredients for which only deodorant claims are made are classified legally as cosmetics rather than drugs. These products are formulated with ingredients which have been placed in Category III by the Panel but which will be moved to Category I or II at the end of the period allowed for submission of data to prove safety and effectiveness. These products are now in Category III but might be moved into Category II in the future, if the Food and Drug Administration concludes from the data before it that they are not generally recognized as safe and effective. However, the data might not support a finding that they are adulterated cosmetics, thus there is a risk that these products may continue to be marketed as cosmetics without adequate substantiation of safety.

Regardless of the legal classification of these products, it is important from a public health standpoint that they be subject to the same strict requirements for safety and effectiveness as the drug products which the Panel has reviewed in this Report.

As long as the antimicrobial ingredients of these products are effectively regulated, the Panel is not concerned whether they be classified as cosmetics or as drugs. If, for example, a regulation can be promulgated imposing the kind of testing requirements recommended in this Report upon all cosmetics containing antimicrobial agents at levels higher than those necessary for preservative use, the Panel's concerns will be met. If it is not possible adequately to control products classified as cosmetics in this way, then the Panel would strongly recommend that the Food and Drug Administration institute whatever action is necessary to reclassify cosmetic products containing antimicrobial agents as drugs.

In the view of the Panel, the Food and Drug Administration should take this regulatory action in the near future. If it turns out that the Food and Drug Administration has no legal basis to require that cosmetic products containing antimicrobial ingredients be adequately tested for safety, the Panel would urge Congress to furnish the necessary authority.

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2. *Efficacy for erythrasma.* Definite evidence has been presented for the therapeutic effectiveness of antimicrobial-containing soaps against erythrasma.

Erythrasma is a skin disease caused by *Corynebacterium minutissimum.* This skin microorganism has been identified by Sarkany et al. (Ref. 1, 2 and 3) and Gougerot and Duche (Ref. 4).

While definitive evidence was presented for the therapeutic effectiveness of antimicrobial-containing soap against this disease by Kooistra (Ref. 5), Dodge et al. (Ref. 6), Rosenberg and Allen (Ref. 7), Taber et al. (Ref. 8) and Taplin et al. (Ref. 9), the Panel agreed that this observation alone could not support claims of antimicrobial activity against other infections. Erythrasma cannot be diagnosed except by a physician using special techniques and therefore, OTC use and labeling would not be appropriate.

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3. *Effectiveness of surgical hand scrubs containing antimicrobials.* Since Semmelweis' mandate in the period 1841–1846, published in 1861 (Ref. 1), that the physician's examining fingers be washed and disinfected with chlorine to prevent childbed fever, there has been controversy surrounding the desirability of disinfection of the surgeon's hands. The intervening years have produced only a little evidence to clarify the situation. Price's work in 1938 (Ref. 2) initiated attempts to quantify reduction in the microbial flora. The picture has become more confused with the introduction of new antimicrobial agents, particularly those with a substantive effect. A substantive effect is the retention or binding of the chemical in the stratum corneum of the skin after rinsing.

Historically, the effectiveness of a surgical scrub product has been judged by the reduction in microbial count achieved after the use of the scrub. These handwashing tests have usually been performed utilizing one of the several basin tests described by Price (Ref. 2), Cade (Ref. 3) and Quinn (Ref. 4).

In the past, the single criterion for effectiveness of a surgical scrub product has been a comparison of the microbial count on the hands before and after handwashing. The comparison has usually been made from the results of these standard handwashing tests. The Glove Juice Test (see guidelines for testing), included in the suggested protocols, is an improved test which the Panel feels is necessary to evaluate two aspects of microbial reduction in the efficacy testing of surgical hand scrubs: the initial reduction of microbial count (as measured before and after hand scrubbing) and, in addition, any subsequent build-up of microbial count over time. The increase in count is measured by a comparison of the baseline count and/or the reduced count, after scrubbing, with the count determined at a selected time period after donning surgical gloves.

The use of surgical antiseptics dates back to Semmelweis and Lister. The latter disinfected the skin at the operative site, dressings, and instruments in a 1:20 solution of carbolic acid, and degermed the hands. Godlee (Ref. 5) has recorded the historical aspects of the development of Lister's methods. In more recent times, tincture of green soap followed by alcohol rinse was in common usage until the 1950's. Since then, surgical scrubs containing an iodophor or hexachlorophene have been in common usage, as reported in a survey by King and Zimmerman (Ref. 9). Iodine scrubs in the form of iodophor formulations have been widely accepted. Polyvinyl pyrrolidone and various surfactant carriers are used to slow iodine release and thus reduce the irritation of the skin caused by iodine. The activity of any iodophor is dependent on the release of titratable iodine from the complex. The iodine released when the complex is in contact with the skin is not only available to kill micro-organisms, but is only available and is adsorbed by dead skin cells or other organic material on the skin. The action of iodine is broad spectrum, including gram positive and gram negative micro-organisms, fungi and viruses.

Data delineating the balance between the release of iodine from an iodophor and availability to the microorganisms on the skin were not submitted and are required before unequivocal judgment concerning the effectiveness of iodophors on the skin can be made. Iodophors usually do not possess any substantivity.

It is desirable for surgical hand scrubs to contain substantive antimicrobials. Although hexachlorophene is substantive, especially with repeated use, its toxicity is of such concern to the Panel that they recommend that an alternative should be sought. While a one-time scrub with a substantive antimicrobial may not reduce the count initially as low as an iodophor, or indeed, any lower than scrubbing with soap and water, repeated use does reduce the level of the microbial flora on the skin. Three to five days are usually required to demonstrate the substantive activity of these products. The action of a substantive product may also reduce the rapidity with which the count rises after the surgeon's gloves are donned. The assumption should be verified using the Glove Juice Protocol.

Actually, while products formulated with either fast-acting or substantive antimicrobials possess attractive characteristics, neither one alone possesses ideal characteristics for a surgical hand scrub. The obvious solution, where chemical compatabilities permit, is a combination of the use of both products. The consistent use of a substantive antimicrobial-containing product daily at home and in the hospital would yield a reduced level of flora and some substantivity on the skin. Scrubbing with an iodophor would reduce the flora to an even lower level prior to surgery. The substantive characteristic might also be made available in a glove powder, lotion, or foam to be applied to the hands prior to donning the gloves.

The proof that one surgical hand scrub, or for that matter, any surgical hand scrub is effective as a prophylaxis for post surgical infection would be ideal; however, the data are probably impossible to acquire since there are multiple factors involved in post-surgical infection. The concept of reducing the microbial count to as low a level as possible is certainly prudent, since the longer the surgery, the greater the risk to the patient from post-surgical infection.

The punctured surgeon's glove has been hypothesized, and in some cases shown, to be the source of post-surgical wound infection, as reported by Devenish and Miles. (Ref. 6). It is estimated that between one-third and one-half of the surgical gloves are punctured or torn during surgery.

From the results of research on skin flora, it is now apparent that wearing of occlusive surgical gloves or wrapping

the skin with occlusive plastic allows the growth of high populations of microorganisms and has been described by Marples (Ref. 7) and Peterson (Ref. 8). The Panel, therefore, recognizes that donning of the surgical glove may itself produce a rapid increase in microbial count on the hands, even after a surgical scrub product has been used.

Considering these facts, the Panel feels that an effective surgical scrub should reduce the initial count of both the transient and normal flora to as low a level as possible and prevent the build-up of high microbial counts in the glove with time. The exact shape of the curve indicating increase in microbial count with time after the use of a fast-acting scrub or a substantive antimicrobial scrub has not yet been determined.

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4. *Use of health-care personnel handwash.* The overriding reason for the washing and degerming of the hands of nursing and other hospital personnel is the prevention of the transfer of pathogenic organisms from infected patients to the attending personnel and to other patients.

The development and testing of products for this purpose has lagged. The ideal preparation would be a broad-spectrum, fast-acting, substantive antimicrobial which could realistically be used for the numerous repeated daily handwashings required in patient care. The ideal product must reduce the transient flora to the level present before the manipulations required by patient care and must have characteristics which will allow repeated use and conformity to routine use without excessive irritation.

Transient microorganisms can be readily added to the flora of the skin and be retained for varying periods of time depending on the environmental and micro-environmental conditions encountered. The variety of transient organisms acquired depends upon the contacts which the hands have made. Organisms encountered and retained on the skin have been enumerated and described by Marples (Ref. 1), Blank et al. (Ref. 2) and Rosebury (Ref. 3) and include numerous gram negative species (Ref. 6) and a variety of fungi.

The plea was first made by Price in 1950 (Ref. 4) and repeated by King and Zimmerman (Ref. 5) for a comparative study of hand degerming and scrubbing products using standard laboratory techniques so that some rational recommendation for use can be made. This Panel would also recommend controlled comparative studies in an attempt to reduce the conflicting and ambiguous claims by manufacturers and possibly to resolve laboratory data from studies where the design varies virtually with every study performed.

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5. *Use of pre-operative skin preparations.* An antimicrobial product for use in the preparation of the operative site may possess characteristics different from surgical scrubs or handwashing products. Since the product is normally and routinely applied only once to prepare the skin for surgery or manipulative procedures, the antimicrobial should be fast acting and broad spectrum. The product should not cause injury to the site where it is applied. It is desirable to reduce the microbial population (resident and transient) to as low a level as possible prior to the surgical procedures (Ref. 2). Five percent phenol solution was preferred by Lister, while iodine, organic mercury compounds, quaternary ammonium compounds and ethyl alcohol have been used in more recent times as recorded by King and Zimmerman (Ref. 1).

There are some difficulties associated with the testing of pre-operative skin preparations. (See discussion in the guidelines of efficacy testing of a patient pre-operative skin preparation.) Frequently, the skin is not rinsed after application of a pre-operative skin preparation. If in vivo tests of effectiveness are undertaken, the carry-over of the residual antimicrobial ingredient from the skin to the culture medium in the process of sampling of the skin becomes a problem. In order to counteract the antimicrobial activity of any chemical inadvertently carried-over, neutralizers specific for the antimicrobial should be added to the culture medium. Neutralizer development has made reliable testing of antiseptics and disinfectants possible. The lack of rinsing of the skin and the subsequent carry-over of the antimicrobial ingredient during testing has stimulated development of a variety of neutralizing formulations for use in the testing of antimicrobial skin products including a universal one as described by Engley and Dey (Ref. 3). If neutralizers are utilized, the inherent toxicity of the neutralizer for the specific mircroorganisms being tested should be determined, as well as verification that the neutralizer is effective for the antimicrobial chemical being tested. Effectiveness testing of a Patient Pre-Operative Skin Preparation is described in the Guidelines for Testing in this document.

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6. *Use of antimicrobial products in the reduction of staphylococcal colonization in the nursery.* Studies by Rammelkamp et al. (Ref. 1), Love et al. (Ref. 2) and others, have shown a reduction in the incidence of pathogenic organisms in the nursery with antiseptic hand care. Gluck and Wood (Ref. 3) showed, in a controlled study, that routine practice of hexachlorophene bathing of newborn infants in the nursery reduced staphylococcal colonization. Many washing procedures for infants utilizing dilutions of the commonly available 3 percent hexachlorophene products with variations in regimen have been in use since hexachlorophene bathing was introduced.

Questions have been raised over the years concerning the influence of the use of a gram positive bacteriostatic agent on the incidence of gram negative infections in the nursery. One such comment is in the report by Light and Sutherland (Ref. 4). Some nurseries have operated without the use of hexachlorophene bathing at all and still maintain low infection rates. Indications are that the recent cessation of use of hexachlorophene to bathe infants in the nursery has resulted in increased staphylococcal infections in nurseries. These outbreaks have been documented by Gezon (Ref. 5), Dixon et al. (Ref. 6) and Kaslow et al. (Ref. 7).

The Food and Drug Administration, upon the advice of the OTC Antimicrobial I Panel, took action and issued in the FEDERAL REGISTER of September 27, 1972 (37 FR 20160) a final order making hexachlorophene available only by prescrip-

tion, except at concentrations less than 0.1 percent as part of a preservative system, and limiting the indications in the labeling under 21 CFR 3.91. The use of hexachlorophene in nurseries is now limited to handwashing by personnel and its use to bathe the infants is recommended only in the face of an unchecked staphylococcal outbreak. The indications as specified in the final regulation are as follows:

(a) Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.

(b) For topical application to control an outbreak of gram positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

Other antimicrobial products may eventually replace hexachlorophene as a means of reducing staphylococcal colonization. Authors generally agree that the umbilical stump is the site initially colonized with *Staphylococcus* in the newborn. This observation has been verified by Hurst (Ref. 8) and Fairchild (Ref. 9).

Studies designed to show reduction in colonization with staphylococci and subsequent prevention of staphylococcal disease will be difficult to perform in the future with new antimicrobial products. The major difficulties are the projected large number of patients necessary for a prospective study and the need to obtain patient consent.

The Panel has reviewed triple dye (a combination of bacteriostatic dyes) which was in use prior to the introduction of hexachlorophene bathing of neonates (Ref. 10). This dye combination has been used to supplant the formerly used hexachlorophene (Ref. 11). Because of the renewed interest in Triple Dye, the Panel has reviewed the existing literature and has included this product in the report.

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7. Use of skin wound cleanser. The removal of foreign material from minor, superficial wounds without retardation of healing is regarded by the Panel as the primary use for this category of products.

The Panel is aware that there is a wide array of products which are to be used on the skin for cleansing wounds or with the intent of preventing infections. Historically these products have contained an antimicrobial ingredient based on the theory that use of such an ingredient was beneficial for use in or on a minor cut, scrape, burn or wound. Little, if any, scientific evidence exists to substantiate the assumption of prophylaxis against infection by the topical use of antimicrobial ingredients.

The Panel, after review of the information submitted, has concluded that the primary treatment of the wound should be the thorough cleansing of that wound to remove foreign material, dirt and debris.

STATEMENT ON SAFETY FACTORS FOR TOPICALLY APPLIED ANTIMICROBIAL AGENTS

In the field of toxicology it has been traditional in estimating safety factors for topically applied materials to relate the "effect" and "no-effect" level resulting in pathological alterations from the orally (intravenous, intraperitoneal and inhalation have also been used) and dermally administered dose. Some multiple of the highest no-effect dose, based on body weight (mg/kg), has been used in calculating a safety factor. The Panel in considering this approach to safety factors examined other evidence that suggested that biological effects of the applied chemical are often best extrapolated among species on the basis of relative surface areas (Ref. 2 and 10). The Panel utilized this latter approach initially in its calculations for safety factors for topically applied antimicrobial ingredients. In addition, the Panel is cognizant of the fact that analytical chemical techniques can now be utilized to determine concentrations of chemicals in blood. This then can permit correlation of the topically applied dose to blood levels and any resultant pathological alterations.

Knowledge of the blood levels achieved by application of a chemical in varying formulations at different dose levels and routes of administration can help in the understanding of the biopharmacology of a chemical substance. Even before the topically applied material gets into the blood there are many conditions which influence the rate and amount absorbed through the skin. There are great differences among animal species, among skin areas on the body, among normal, irritated, diseased or previously treated skin areas and often variations from one individual to another. For these reasons systemic toxicological information from topically applied materials can at best be only supplementary to that from administration by another route which bypasses the cutaneous barrier and insures appropriate amounts in the blood. Additionally, the rate of absorption, the rate of excretion, the metabolic fate, and the amount stored in depots also affect the relationship between the applied dose and pathological alteration. Blood levels therefore may be a more reliable correlate of pathologic effects to aid in the determination of safety factors than administered dosages. The Panel believes that it is important to develop, such information whenever possible, and to take it into consideration in the development and setting of safety factors. This blood level data should be required in toxicological studies as it may be a more direct measure of absorbed dose than can be obtained from merely a measure of topically applied dose.

Many methods were presented to the Panel for the determination and/or prediction of the toxicity of an active chemical ingredient in man based on data obtained from laboratory animals.

A variety of calculations of applied dose, absorption, blood levels and appropriate safety factors have been reviewed by the Panel and discussed with various persons. The Panel has decided to detail specific examples of their calculation procedures used in the estimation of possible toxic effects among species, and they are included herein. The Panel recognizes the difficulty in the translation of the results of toxicity testing from one species to another and particularly, to man. Various assumptions have been made in the past concerning the relative sensitivity of man compared to various animal species, but established comparisons do not exist primarily because of variation in effect with different drugs.

Paracelsus (1493–1541) wrote: "All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing a poison." In addition to the "poisonous qualities" a chemical may possess, at certain concentrations and routes of administration, other characteristics such as subject idiosyncrasy, allergy, and tolerance must be considered to evaluate safety of an effective dose.

The initial toxicological evaluations are conducted in animals to determine the qualitative and quantitative pharmacological aspects of the chemical. Delineators of response which may vary from species to species are routes of adminis-

tration, dose and plasma levels, rate of absorption, rate and route of excretion, distribution throughout the body, and nature and number of metabolites. Because species differences can be considerable, multiple animal species (rodent and nonrodent) should be used. Further, something should be known of the effect of the active chemical agent in all the species tested so that some comparison can be made with man.

Blood levels of the active ingredient in animals are of value in the overall evaluations of "effect" (lowest dose which produces a toxic effect) "no-effect" (highest dose which produces no toxic effect) response dose levels. They are the result of several interrelated mechanisms, among them being (1) absorption rate from the site of application, (2) metabolism by enzymes, (3) distribution and storage in the tissues, and (4) excretion. Absorption is not the same in all animals or from all sites of administration. This may be related to species differences and/or to the physical-chemical properties of the active chemical. The metabolic rate and fate of an ingredient is a direct reflection of the animals' enzyme systems which characterize the individual animal species. Therefore, blood levels of the active chemical and or metabolites are important determinants after a particular mode of dosing in a particular species of animal. As demonstrated by Spinks (Ref. 1) when 100 mg/kg of sulfadimidine was fed orally to 10 different species of animals, doses produced blood levels in the various species which had little relationship to body size or blood volume. As stated earlier, absorption is not the same in all animals, or from all sites of administration. Of course, experienced investigators would shave the site of application for the testing of topically applied products and dose seven days a week.

The active ingredients which are reviewed here are formulated in topically applied products. The importance of vehicle in the delivery of the active ingredient is well recognized. Not only should there be an investigation of toxic effect after topical application, but the character and effect of the vehicles alone should also be examined. The toxicity of a specific ingredient can be dramatically affected by selection of a vehicle.

The Panel recognizes the difficulty in translating the results of animal toxicity to man. Sufficient animal data must be collected to construct a dose/response curve. This should include adequate data on absorption, blood level(s), metabolic rate and fate, and excretion, so that an analysis for threshold effect and safe use level for that particular animal can be determined. Then an extrapolation to man may be made. Any error in translation of effects to man must be on the side of human safety. A safety factor frequently has been applied to the lowest effect level in animals when that particular dose is translated to potential and/or possible toxic effects in man. For example, a 100-fold safety factor has generally been used for the applied dose for food additives. Actually, it varies from 10 to 500 in application to food additives. The safety factor used in any given case depends upon the nature of the adverse effects noted in animals and on the amount of data derived from human studies. The 100-fold margin of safety is a useful general guide. If, however, a different safety factor is used, it should be based on adequate scientific studies that establish safe levels of use. The Panel has used the methods of Paget and Barnes (Ref. 2) to translate toxic oral or topical doses in animals to the dose where an expected toxic effect might appear in man. This was done because safety data of the type recommended by the Panel were not available.

The following methods were used by the Panel in an effort to calculate these safety factors:

The Panel made calculations from data presented for various ingredients. The calculations presented here are hypothetical, show the assumptions made and are intended to explain the method.

1. Expected no-effect dose level in man: Determine the lowest toxic effect and the highest no-effect dose in mg/kg topically applied in an animal species. (If an effect cannot be determined in a topical application, the oral route of administration should be employed). Take the highest no-effect dose in that animal species and calculate the absolute dose using the method described in Paget and Barnes (Ref. 2). From the absolute dose the multiplication can be made with the factor given in this reference for the specific animal used in the test and this, then, is the dose level at which no-effect might also be expected in man.

2. Expected blood level from product use in man: Assume a bar soap with 3 percent active antimicrobial is used for one bath per day. Assume that 7 grams of soap are used in one bath. This would give an exposure of 0.21 grams or 210 mg. per bath of active ingredient. Assume retention of all 210 mg. active ingredient on the skin (there is very little firm data presently available on the amount of antimicrobial retained on the skin after exposure). If 3 percent of the applied active ingredient is absorbed into the blood stream, the dose per bath would be:

0.03×210.0 mg. = 6.30 mg. active ingredient absorbed.

If the assumption is made that the total dose is immediately absorbed, the dose distributed in the blood of a 70 kg. human would be:

$$\frac{6.30 \text{ mg}}{5{,}000 \text{ ml blood}/70 \text{ kg human}} = 1.26 \text{ mcg active ingredient per milliliter of blood}$$

The assumption is made here that the amount of chemical presented to the individual in a single bath is all retained on the skin and absorbed and distributed in the blood giving a blood level of 1.26 mcg/ml.

As a further example, assuming retention of 0.5 mcg. of active ingredient per sq. cm. of skin and the product is to be used over the entire skin area, as in a bar soap, the total dose retained would be 9.25 mg. over the entire body. The calculation would be 0.5 mcg. per sq. cm. $\times$18,500 sq. cm. of skin (based on a 70 kg, 5'10" human). Assuming for this case, a 10 percent absorption:

$9.25 \text{ mg.} \times 0.10 = 0.93 \text{ mg. dose per bath}$

If the assumption is also made that the total dose is immediately absorbed, the dose distributed in the blood of a 70 kg. human would be:

$$\frac{0.93 \text{ mg}}{5{,}000 \text{ ml blood}/70 \text{ kg human}} = 0.18 \text{ mcg active ingredient per milliliter of blood}$$

Safety factors were calculated using the available evidence. For the specific calculations, see the individual ingredient statements.

These two hypothetical calculations using known facts with stated assumption are examples of the type of safety factor calculations considered by the Panel. In this calculation, the information required is the retention of the chemical by the skin after exposure. The missing information here is the absorption excretion kinetics for that chemical.

A direct comparison can be made and thus a safety factor can be estimated by a comparison of the calculated human blood level with the blood level in animals, if known. A comparison of the dose where there is no effect in animals translated to the dose in which no effect may be expected in humans against the hypothetical dose to which a person is exposed from the use of a product containing the ingredient can be made if blood level data are not available.

It must be stressed again that the best calculations and judgments are made when all of the pertinent data are available and frequent assumptions do not have to be made. The variety of calculations presented to the Panel have been the result of making assumptions because the data were not available.

In the Panel's judgment, submitted studies to determine effect/no-effect level have been inadequate. For example, where two dose levels were run (100 mg/kg; 500 mg/kg) and the lower dose demonstrated no-effect while the higher dose demonstrated an effect, additional studies must be conducted using appropriate intermediate doses to determine the highest no-effect level.

If the safety factor is extrapolated from an animal species to man, considering surface area, the highest no-effect dose should be used for the multiplier. In the absence of complete data, at least a one hundred-fold safety factor should be applied when translating the animal highest no-effect dose to man.

The ideal situation would occur where enough animal data have been collected to construct a dose response curve with concurrent blood levels so that analysis for threshold effect and safe level estimation for the animal can be made Mantel and Bryan (Ref. 3), Mantel (Ref. 4)

and Gross et al. (Ref. 5). Additional references supporting the ideas expressed here are found in Crampton (Ref. 6), Litchfield (Ref. 7 and 8) and World Health Organization Technical Report (Ref. 9).

In summary, the Panel recommends that toxicological studies, where appropriate, contain applicable administered doses, achieved blood levels, and observed pathological alterations in the same study and the same species.

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DEFINITIONS OF PRODUCT CATEGORIES

Not all antimicrobial products are used for the same purpose nor should the requirements for effectiveness be the same. In an attempt to classify topically applied antimicrobial ingredients and products, one of the important concepts considered in the development of definitions is the distinction between the determination of effectiveness in preventing or combatting clinical infection (sepsis) and the reduction of resident or transient microorganisms on the skin.

Label claims for handwashing, surgical scrubs and first-aid products presently include prevention of infection, reduction in spread of infection, and reduction of normal flora. Frequently, claims against specific organisms are made with clinical implications based solely on in vitro data.

The following specific definitions of antimicrobial product categories have been developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion.

The most rigid definition with respect to effectiveness requirements is for a "skin antiseptic". The other six definitions relate to the "skin antiseptic" definition and their distinctive effectiveness requirements are described. Each defined product requires specific studies to support effectiveness.

The Panel has adopted definitions for the following categories of topical preparations when applied at acceptable use concentrations:

Skin Antiseptic
Patient Pre-Operative Skin Preparation
Surgical Hand Scrub
Health-Care Personnel Handwash
Skin Wound Cleanser
Skin Wound Protectant
Antimicrobial Soap

1. Skin antiseptic—"A safe, non-irritating, antimicrobial-containing preparation which prevents overt skin infection. Claims stating or implying an effect against microorganisms must be supported by controlled human studies which demonstrate prevention of infection."

There has been misunderstanding, confusion and exaggeration in the definition and use of the term "antiseptic." The literal translation from the Greek means "against putrefaction." In recent times the definition has been interpreted as activity against infection or microbial sepsis. The term "antiseptic" is comparable to accepted definitions for a "disinfectant." Even though they are often confused, there has been a traditional restriction of the term "antiseptic" for antimicrobial formulations applied to living tissues, particularly on the human body, and the term "disinfectant" to inanimate objects. The distinction between antiseptics and disinfectants, for regulatory purposes, has also been made on the basis of these definitions. The Panel's view is that "antisepsis" properly refers to the use of antimicrobial chemicals on the skin or on human tissue and that "disinfection" properly refers to their use on inanimate objects. Disinfectants or antimicrobial chemicals labeled for use on inanimate objects are regulated as economic poisons under the Federal Environmental Pesticide Control Act (7 U.S.C. 136). Antiseptics labeled for use on human or animal tissue are regulated as drugs under the Federal Food, Drug and Cosmetic Act.

The traditionally accepted definition metic Act defines an "antiseptic" as "The representation of a drug in its labeling as an antiseptic shall be considered to be a representation that it is a germicide except in the case of a drug purporting to be or represented as an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder or such other use as involves prolonged contact with the body."

The traditionally accepted definition of an antiseptic by the scientific community has included activity against infection when applied to living human tissues and has been recorded in publications by Reddish (Ref. 1) and Patterson (Ref. 2). A current definition by Sykes (Ref. 3) states that antiseptics are preparations possessing antibacterial or antifungal activities which are suitable for application to living tissues of the human body.

Over the years, the exaggerated labeling claims on a large variety of products containing antimicrobials has led to misuse and abuse of the term "antiseptic."

The Panel has attempted to eliminate the confusion by developing a rigorous definition of a Skin Antiseptic. The remaining definitions can be explained in terms of their own effectiveness requirements and in the manner in which their use and composition differs from a skin antiseptic.

2. Patient pre-operative skin preparation—"A safe, fast-acting, broad-spectrum antimicrobial-containing preparation which significantly reduces the number of microorganisms on intact skin."

Any product labeled as a Patient Pre-Operative Skin Preparation must be effective against all types of organisms comprising the skin microflora so as to obtain as low a number of micro-organisms as possible in a short period of time without injury to the operative site. Controlled studies, conclusively demonstrating that the use of antimicrobial-containing products are superior to soap and water in the prevention of post-surgical wound infections do not exist. The inescapable logic in the use of products designed to reduce the microbial flora in the operative field is apparent and is supported by a long history of use. The use of these products is specialized, under professional supervision, and will generally be for a single application.

3. Surgical hand scrub—"A safe, non-irritating antimicrobial-containing preparation which significantly reduces the number of micro-organisms on the intact skin. A surgical hand scrub should be broad-spectrum, fast-acting and persistent."

The use of this category of products is normally limited to the hands and forearms. The comments concerning post-surgical infection made under Patient Pre-Operative Skin Preparation apply here. A discussion of the effectiveness, difficulties to be considered and rationale for the product is presented in the Panel's comment concerning effectiveness under Surgical Hand Scrub. The term persistent refers to the possibility of extended activity with time of an applied antimicrobial by a mode, including among others, substantivity.

4. Health-care personnel handwash—"A safe, non-irritating preparation designed for frequent use, which reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing and drying. If the preparation contains an antimicrobial agent, it should be broad-spectrum, fast-acting, and if possible, persistent."

A product fitting this definition should be designed to be used repeatedly, perhaps as many as 100 times a day, to reduce and, if possible, eliminate "transient" microorganisms present on the

skin resulting from contact with contaminated persons or materials. In all likelihood, the specified effect, i.e., removal of transient organisms can be achieved with a well-formulated nonantimicrobial soap or detergent product. In vivo testing would be mandatory to show the effectiveness of such a product (See suggested testing procedures in Guidelines in this document). Any transient organism can become part of the established "resident" flora with time. Obviously, in a health-care situation, the fast, effective removal of transient organisms is a requirement since they may be pathogenic.

Such products containing an antimicrobial ingredient should be broad-spectrum. The term broad-spectrum when used with reference to microbiological spectrum means that the antimicrobial has activity against more than one type of microorganism. For example, many of the active ingredients discussed in this report have significant activity against only gram positive bacteria whereas a broad-spectrum antimicrobial would have to demonstrate activity against gram positive and gram negative bacteria and would very likely also have activity against fungi and viruses. A product containing an antimicrobial with substantive (retention of the chemical in the skin) properties which acts to prevent the growth or establishment of transient microorganisms as part of the normal baseline or resident flora would provide an added benefit.

Essential qualities of all health-care personnel handwash preparations must be low toxicity and little or no irritancy with repeated use. The adherence to washing regimens is an important consideration in the formulation of products in this category and health care personnel reject the repeated use of irritating and/or unpleasant formulations.

5. Skin wound cleanser—"A safe, nonirritating liquid preparation (or product to be used with water) which assists in the removal of foreign material from small superficial wounds and does not delay wound healing."

A product in this category is designed to aid, by its cleansing activity, in the removal of foreign materials from a minor superficial wound. Such a product may or may not contain an antimicrobial ingredient. Included in the term "safe" are the considerations that the skin wound cleanser should be non-irritating and not delay wound healing. It is obvious that a product such as a bar soap with water could serve as a Skin Wound Cleanser. There is no necessity that such a product show effectiveness in the prevention of wound infection.

6. Skin wound protectant—"A safe, non-irritating preparation applied to small cleansed wounds which provides a protective (physical and/or chemical) barrier and neither delays healing nor favors the growth of microorganisms."

A product in this category whether a liquid, semisolid, or solid preparation, when applied to a properly pre-cleansed superficial minor wound, provides a physical and/or chemical barrier to protect the wound from further contamination with foreign material or microorganisms. This type of product may or may not contain an antimicrobial ingredient. These products, by definition, are not designed for extended repeated use or for use on large or deep wounds.

7. Antimicrobial soap—"A soap containing an active ingredient with in vitro and in vivo activity against skin microorganisms."

Soaps without antimicrobial ingredients (as defined in 21 CFR 3.652) are exempt from regulation under the Federal Food, Drug, and Cosmetic Act.

An antimicrobial soap must, by definition, contain an active antimicrobial ingredient. A product in this category is designed to reduce the microbial flora of the skin. Both the resident and transient pathogenic and non-pathogenic flora of the skin may be reduced by the use of an antimicrobial soap. The relationship of this reduction to the prevention of minor skin infection has not been established. (For a more detailed review, see the Panel's comments on the effectiveness of Antimicrobial soaps.) Antimicrobial soaps should be designed and tested for safety, when used repeatedly and for extended periods, potentially for a lifelong duration with total body exposure. In recent years the addition of antimicrobial agents to soaps has greatly increased, and many individuals are involuntarily, unknowing captive consumers of such soaps (Ref. 4). Because a large portion of the population is exposed to this potential hazard, the Panel recommends that any soap or detergent containing an active antimicrobial ingredient state on its label the United States Adopted Names (USAN) or common name of the active ingredient.

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The OTC Antimicrobial I Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through June 15, 1973 in arriving at its conclusions and recommendations.

ACTIVE INGREDIENTS

The Panel reviewed all active ingredients which were the subject of submissions made to the Panel pursuant to the standards for safety, effectiveness, and labeling set out in the regulations.

In accordance with the regulations, the Panel's findings with respect to these ingredients are set out in three categories:

I. Conditions under which antimicrobial products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which antimicrobial products are not generally recognized as safe and effective or are misbranded.

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

A table listing the active ingredients, classified into one of the three categories, for use in preparations defined by the Panel is included for easy reference.

	Active ingredient	Antimicrobial soap	Healthcare personnel hand wash	Patient preop skin preparation	Skin antiseptic	Skin wound cleanser	Skin wound protectant	Surgical hand scrub
1	Benzalkonium chloride	NA[1]	III	III	III	I	III	III
2	Benzethonium chloride	NA[1]	III	III	III	I	III	III
3	Cloflucarban	III	III	II	II	II[2]	II	II
4	Fluorosalan	II	II	II	II	II	II	II
5	Hexachlorophene	II	II	II	II	II	II	II
6	Hexylresorcinol	NA[1]	III	III	III	I	III	III
7	Iodine complexed with phosphate ester of alkyl-aryloxy polyethylene glycol.	NA[1]	III	III	III	III	III	III
8	Methylbenzethonium chloride.	NA[1]	III	III	III	I	III	III
9	Nonylphenoxypoly (ethyleneoxy) ethanoliodine.	NA[1]	III	III	III	III	III	III
10	Para-chlorometaxylenol	III	III	III	III	III	III	III
11	Phenol:							
	(a) Greater than 1.5% (aqueous alcoholic)	II	II	II	II	II	II	II
	(b) 1.5% or less (aqueous alcoholic)	III	III	III	III	III	III	III
12	Poloxamer-iodine complex	NA[1]	III	III	III	III	III	III
13	Povidone-iodine complex	NA[1]	III	III	III	III	III	III
14	Tincture of iodine	NA[1]	II	I	II	II	II	II
15	Tribromsalan	II	II	II	II	II	II	II
16	Triclocarban	III	III	II	II	II[2]	II	II
17	Triclosan	III	II	II	III	III	III	II
18	Triple dye	NA[1]	NA[1]	NA[1]	III[3]	NA[1]	NA[1]	NA[1]
19	Undecoylium chloride-iodine complex.	NA[1]	III	III	III	III	III	III

[1] NA (Not applicable)—Due to a physical and/or chemical incompatability in formulation.
[2] Classified in category III when formulated in a bar soap to be used with water.
[3] Restricted for use only in the neonatal nursery.

NOTE.—For other phenols and vehicles, see body of report.

I. *Conditions under which antimicrobial product are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the conditions specified in Category I be made effective 30 days after publication of the final monograph in the FEDERAL REGISTER.

ACTIVE INGREDIENT

A. The active ingredients generally recognized as safe and effective for use in an "antimicrobial soap" and not misbranded are:

1. None listed.

B. The active ingredients generally recognized as safe and effective for use in a "health-care personnel handwash" and not misbranded are:

1. None listed.

C. The active ingredients generally recognized as safe and effective for use in a "patient pre-operative skin preparation" and not misbranded are:

1. Tincture of Iodine.

D. The active ingredients generally recognized as safe and effective for use in a "skin antiseptic" and not misbranded are:

1. None listed.

E. The active ingredients generally recognized as safe and effective for use in a "skin wound cleanser" and not misbranded are:

1. Benzalkonium chloride.
2. Benzethonium chloride.
3. Hexylresorcinol.
4. Methylbenzethonium chloride.

F. The active ingredients recognized as safe and effective for use in a "skin wound protectant" and not misbranded are:

1. None listed.

G. The active ingredients generally recognized as safe and effective for use in a "surgical hand scrub" and not misbranded are:

1. None listed.

TINCTURE OF IODINE AS A PATIENT PRE-OPERATIVE SKIN PREPARATION

There is an approximate 50-year history of the use of elemental iodine on the skin and mucous membranes. Iodine is soluble in alcohol and only slightly soluble in water but the presence of iodides increases its solubility in water. Iodine is a microbiocidal agent for cells on the skin at low concentrations. It must be recognized that the activity of iodine is dramatically influenced by the presence of organic material. A tincture product containing approximately 2 percent iodine has been used for many years. There is some irritation of the skin associated with the use of tincture of iodine. On the basis of risk-benefit considerations, the one-time use of this formulation as a patient pre-operative skin preparation can, in the Panel's view, be justified considering the efficacy of tincture of iodine on the microorganisms on the skin. The use of this formulation is limited to painting of the operative site prior to surgery and must be removed immediately upon drying with 70 percent alcohol after application, or used as directed by a physician.

The acceptable composition for tincture of iodine is not less than 1.8 grams and not more than 2.2 grams of iodine (I), and not less than 2.1 grams and not more than 2.6 grams of sodium iodide (NaI) in each 100 ml. of 44–50 percent ethyl alcohol or an appropriate denatured alcohol.

HEXYLRESORCINOL FOR USE AS A SKIN WOUND CLEANSER

It is obvious to the Panel from their review of the toxicity data in the literature and in the submissions to the Panel that hexylresorcinol is safe for topical use in small superficial wounds. The concentration of hexylresorcinol for use in a skin wound cleanser should be limited to a use concentration not greater than 1/1000. The major reason for the placement of hexylresorcinol in Category III was the paucity of effectiveness data for uses in other topical products. The reader is referred to the discussion of hexylresorcinol under Category III.

QUATERNARY AMMONIUM COMPOUNDS FOR USE AS A SKIN WOUND CLEANSER

Reference is made to the discussion of quaternary ammonium compounds ("quats") under Category III. Because of the reported delay in wound healing with quaternary ammonium compounds in animal model studies reported by Custer et al. (Ref. 1) and Edlich et al. (Ref. 2), only infrequent use in small superficial wounds is recommended by the Panel. Since many "quats" have a detergent action (Ref. 3 and 4) which can aid in the removal of foreign material from a small wound, their use in the formulation of a skin wound cleanser is reasonable, and in the opinion of the Panel, safe. The concentration of the quaternary ammonium compound (as benzalkonium chloride, benzethonium chloride, or methylbenzethonium chloride) should be limited to a use concentration not greater than 1/750. As defined by the Panel, an ingredient formulated in a skin wound cleanser need not possess antimicrobial activity. The dilution recommended for use of "quats" as a skin wound cleanser under Category I is regarded as safe provided that the product is not used repeatedly, covered with occlusive bandaging, or used in deep or extensive wounds.

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LABELING

OTC products which contain active ingredients listed in Category I may use any phrase that is in the definition for that product category or any of the following additional terms:

A. ANTIMICROBIAL SOAP

1. Antimicrobial soap.
2. Antibacterial soap.
3. Reduces odor.
4. Deodorant soap.

B. HEALTH-CARE PERSONNEL HANDWASH

1. Decreases bacteria on skin.
2. Reduces risk (and/or chance) of cross-infection.
3. Recommended for repeated use.

C. PATIENT PRE-OPERATIVE SKIN PREPARATION

1. Kills microorganisms.
2. Reduces the number of microorganisms on the treated area.
3. Broad spectrum (if applicable).

D. SKIN ANTISEPTIC

1. Prevents overt skin infection.
2. Controls infection.
3. Degerming.
4. Kills germs.
5. Bacteriostatic and/or bactericidal.
6. Reduces the risk of infection and cross-infection.
7. Microbiocidal.
8. First-aid product.

E. SKIN WOUND CLEANSER

1. To clean superficial wounds.
2. Wash superficial (small) wounds.
3. First-aid product.
4. Aids in removal of foreign materials such as dirt and debris.

F. SKIN WOUND PROTECTANT

1. Protects against contamination.
2. Protects wounds.
3. Protectant.
4. First-aid product.

G. SURGICAL HAND SCRUB

1. Only phrases in definition.

The Panel was concerned that the phrases used in the definitions would not always be easily understood by the ordinary individual. For that reason they believe that the above listed terms are necessary so that OTC drugs will have labeling that is truthful and can be understood by consumers.

II. *Conditions under which antimicrobial products are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the conditions specified in Category II, except for hexachlorophene and tribromsalan which have been handled separately (see hexachlorophene and tribromsalan discussions in this section) be made effective six months after publication of the final monograph in the FEDERAL REGISTER.

ACTIVE INGREDIENTS

A. the active ingredients not generally recognized as safe and effective for use in an "antimicrobial soap" and misbranded are:

1. Fluorosalan.
2. Hexachlorophene.

3. Phenol greater than 1.5 percent aqueous/alcoholic.
4. Tribromsalan.

B. The active ingredients not generally recognized as safe and effective for use in a "health-care personnel handwash" and misbranded are:

1. Fluorosalan.
2. Hexachlorophene.
3. Phenol greater than 1.5 percent aqueous/alcoholic.
4. Tincture of iodine.
5. Tribromsalan.
6. Trichlosan.

C. The active ingredients not generally recognized as safe and effective for use in a "patient pre-operative skin preparation" and misbranded are:

1. Cloflucarban.
2. Fluorosalan.
3. Hexachlorophene.
4. Phenol greater than 1.5 percent aqueous/alcoholic.
5. Tribromsalan.
6. Trichlocarban.
7. Triclosan.

D. The active ingredients not generally recognized as safe and effective for use in a "skin antiseptic" and misbranded are:

1. Cloflucarban.
2. Fluorosalan.
3. Hexaclorophene.
4. Phenol greater than 1.5 percent aqueous/alcoholic.
5. Tincture of iodine.
6. Tribromsalan.
7. Triclocarban.

E. The active ingredients not generally recognized as safe and effective for use in a "skin wound cleanser" and misbranded are:

1. Cloflucarban.[4]
2. Fluorosalan.
3. Hexachlorophene.
4. Phenol greater than 1.5 percent aqueous/alcoholic.
5. Tincture of iodine.
6. Tribromsalan.
7. Triclorcarban.[4]

F. The active ingredients not generally recognized as safe and effective for use in a "skin wound protectant" and misbranded are:

1. Cloflucarban.
2. Fluorosalan.
3. Hexachlorophene.
4. Phenol greater than 1.5 percent aqueous/alcoholic.
5. Tincture of iodine.
6. Tribromsalan.
7. Triclocarban.

G. The active ingredients not generally recognized as safe and effective for use in a "surgical hand scrub" and misbranded are:

1. Cloflucarban.
2. Fluorosalan.
3. Hexachlorophene.
4. Phenol greater than 1.5 percent aqueous/alcoholic.
5. Tincture of iodine.
6. Tribromsalan.
7. Triclocarban.
8. Triclosan.

[4] Classified in Category III when formulated in a bar soap to be used with water.

HEXACHLOROPHENE

1. The OTC Antimicrobial I Panel thoroughly reviewed the submissions, literature and reports and listened to additional testimony from interested parties concerning the safety and effectiveness of hexachlorophene (HCP, 2, 2′ methylenebis (3, 4, 6 trichlorophenol)). The Panel assumed that a topical antimicrobial OTC preparation should have at least a hundred-fold safety factor (applied to the administered dose) when used as directed. The data indicated that, with the presence of 1500 OTC formulations containing hexachlorophene, there would be potential toxicity from use of multiple products by one individual. Therefore, the Panel recommended to the Commissioner that hexachlorophene be considered not safe for general use as an OTC antimicrobial ingredient in man. Accordingly, a regulation, 21 CFR 3.91, delineates the future use of hexachlorophene only as a prescription drug, except when used as part of a preservative system in a concentration no greater than 0.1 percent.

Much of the information which supported this decision is part of the public record and is summarized below.

A key reference by Lockhart (Ref. 1) presents a review of early toxicological studies with hexachlorophene. She reviews the work of Kimbrough and Gaines (Ref. 2) and others who showed that hexachlorophene fed to rats for a few weeks produced central nervous system toxicity which is pathologically characteristic, if not absolutely diagnostic (Ref. 3).

Lesions occurred in the cerebellum, brain stem, and the cord. The tissues showed marked vacuolization of the grey and white matter. This lesion has been termed "status spongiosis" and has been described by Innes (Ref. 4). Virtually identical lesions have been found in the brains of other hexachlorophene-treated laboratory animals such as rabbits, dogs and monkeys as reported by Kimbrough (Ref. 2), Hart (Ref. 5), Curley (Ref. 24) and OTC Volumes 020044–020046, and 020069–020070 (Ref. 6). These lesions are sufficiently characteristic so that a trained neuropathologist can detect them in an examination of coded histopathologic sections. Furthermore, hexachlorophene-treated animals have been used as positive controls in evaluating potential neurotoxicity of other chemically related antimicrobial agents, providing an illustration of the consistency with which these lesions may be produced. (See OTC Volumes 020139 and 020148 (Ref. 6)).

Equally important was the development of an accurate and reliable method for measuring hexachlorophene blood levels by Browning (Ref. 7) and its application to the toxicological studies. As pointed out in the review by Lockhart (Ref. 1 and 11) results of several studies indicate that a blood level of greater than 1 mcg/ml is generally associated with pathological changes in the animal brains.

Lockhart (Ref. 1) also reviews in some detail a report to the Food and Drug Administration of a ninety-day bathing study of newborn rhesus monkeys with 3 percent hexachlorophene emulsion. Compared to no incidence in the controls, all five of the hexachloropohene-treated monkeys developed status spongiosis brain lesions and had mean blood levels about 1 mcg/ml. Other reports have confirmed the toxicity from repeated bathing of rabbits (OTC Volume 020148, Ref. 6) and in newborn monkey bathing studies (Ref. 14). In this study in newborn monkeys (Ref. 14), only seven days exposure was required to induce the lesions. Nieminen et al. (Ref. 25) have shown that hexachlorophene begins to have a toxic effect on the brains of exposed rats after they are about one week old. They noted vacuolization of the white matter, increased brain weight and water content along with paralysis of the hind legs. The new-born rats succumbed to a much lower oral dose of hexachlorophene than older rats. Martin-Bouyer (Ref. 26) has indicated the presence of lesions with electron microscopy as early as two hours after exposure to hexachlorophene. Lockhart (Ref. 1) reported that these toxic effects appear to be reversible in some circumstances after stopping exposure, provided that the animals survive.

In addition, Lockhart (Ref. 11) reviews hexachlorophene toxicity in man. Oral poisoning occurred in a number of cases usually after accidental ingestion. When hexachlorophene was used therapeutically in large doses for treatment of chlonorchiasis for 3 to 6 days, reversible central nervous system and gastrointestinal symptoms were produced in studies reported by Chung et al. (Ref. 8) and Liu et al. (Ref. 9). Topical use of hexachlorophene in the treatment of burns also has resulted in toxic effects and very high blood levels as reported in 1968 by Larson (Ref. 10).

Mullick (Ref. 13) examined the brain tissue sections of four children poisoned by topical exposure to hexachlorophene and confirmed that the lesions were identical to those seen in the animal studies.

Additional evidence of toxicity was reported from France when, during the summer of 1972, it became apparent that many infants had been poisoned by a topical baby powder inadvertently contaminated with up to 6 percent hexachlorophene (Ref. 12). More than 40 babies died during this episode. These data were supplied by the French Government and are currently confidential to the Food and Drug Administration and thus are not part of the public record of this Panel. Nevertheless, it is clear that the blood and tissue of infants who died contained high levels of hexachlorophene, an dthe central nervous system abnormalities observed histologically were indistinguishable from those produced in experimental animals.

While hexachlorophene is adsorbed onto the outer layers of skin, it is also absorbed systemically in relatively small amounts. Approximately 3 percent of the applied dose (in acetone) was absorbed into the systemic circulation in one study by Maibach (Ref. 15).

Significant blood levels have been detected in a number of studies of new-

borns bathed in hexachlorophene preparations, ranging from .009 mcg/ml to 0.78 mcg/ml reported by Curley et al. (Ref. 16 and 24), Cunningham (Ref. 17 and 29), and Kopelman (Ref. 18). In one study of 10 "problem babies," it was found to range from 0.1 to 1.59 mcg/ml with a mean of 0.52 mcg/ml giving toxic levels in some infants. Recent studies over a period of three to four weeks of total body bathing studies with 3 percent hexachlorophene in adults have shown blood levels as high as 1.42 mcg/ml (Ref. 30). Also surgical scrubs of hands and forearms of adults, five times a day, with 3 percent hexachlorophene preparations have given, in selected individuals, levels after 10 days of 0.5 mcg/ml or higher. These findings are a result of a series of blood level studies using a specific hand and arm scrubbing regimen suggested in a Food and Drug Administration protocol. This protocol was used in studies designed to fulfill the requirement for blood level studies for products containing hexachlorophene for continued marketing as prescription drugs. These levels are considered as potentially toxic levels. The highest level recorded from blood level studies using this specific hand and arm scrubbing regimen has been 0.84 mcg/ml. These data are included in OTC Volume 020186 (Ref. 6).

Ulsamer et al. (Ref. 27) measured the hexachlorophene concentrations in the blood of volunteers who used a variety of hexachlorophene-containing products. Blood concentrations ranged from 0.38 mcg/ml. of blood (in an individual using a 3 percent hexachlorophene liquid product on his whole body) to 0.02 to 0.14 mcgm/ml. in subjects only washing their hands with a 3 percent product. They established that routine use of these products produced detectable blood levels, some nearly as high as 0.4 mcg/ml. The number of subjects (12) was small.

A further review by Lockhart (Ref. 28) emphasizes the impact of the demonstration that hexachlorophene applied topically can result in systemic toxicity and the consequences of this information to the regulatory activities of the Food and Drug Administration. The pertinent details of the toxicity resulting from blood levels in animals and the blood levels resuting from use in humans is summarized.

Shuman, Leech and Alvord (Ref. 19 through 22) did a retrospective pathological study of coded brainstem tissue from infants who died of causes unrelated to hexachlorophene which was conducted at two different hospitals, one of which washed all newborns routinely with 3 percent hexachlorophene, while the other did not. Only one of 189 babies not bathed in 3 percent hexachlorophene showed brain lesions characteristic of hexachlorophene toxicity, whereas 20 of 61 babies receiving from one to as many as six hexachlorophene baths showed these brain changes.

Powell et al. (Ref. 23) have reported spongiform changes in myelinated tracts of the brainstem of seven infants with multiple exposures to hexachlorophene. Infants with low birth weight and/or premature infants with broken skin appeared to be a special risk of developing these lesions after hexachlorophene exposure.

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TRIBROMSALAN

2. The OTC Antimicrobial I Panel finds that tribromsalan (TBS, 3, 4', 5 tribromosalicylanilide) cannot be generally recognized as safe for general use as an OTC antimicrobial agent in man.

It is a brominated salicylanilide which even when free of related chemicals can cause photosensitive eruptions in man and its use can result in disabling skin disorders. In addition to the problem of photosensitization, the Panel is concerned about the potential toxicity of this compound, which is intended for daily, total body use, possibly for a lifetime. Animal and human toxicological data made available to the Panel fail to provide a basis for establishment of a safe level for use. With regard to efficacy, there was no clear evidence that it did anything except to help control body odor, for which other safer agents are available.

a. *Toxicology (Animal)*. Although several submissions reported blood levels obtained after varying doses administered both orally and topically, serious discrepancies in the reported toxicity of the drug were not completely resolved. Thus, in rats a report of brain and testicular damage after 25 mg/kg subchronic feeding, OTC volumes 020133 and 020139 was not substantiated in several other studies at higher concentrations, OTC Volumes 020102, 020136 and 020173 (Ref. 1). Two of these studies in which animals were dosed with 500 ppm showed measurable blood levels, but reported no organ toxicity, OTC Volumes 020102 and 020136 (Ref. 1). However, in yet another study, OTC Volume 020163, brain and eye damage was reported at dose levels of 3,750 ppm and questionable changes were seen at 750 and 1000

ppm although similar changes were seen in the controls (Ref. 1). Percutaneous toxicity studies in rabbits generally produced negative results, OTC Volumes 020048, 020107, 020148 and 020156 (Ref. 1). In OTC Volume 020048, in addition, there was a positive control with hexachlorophene which produced brain damage (Ref. 1). However, in the one study showing positive results, the animals were dosed at 1,000 mg/kg by topical application, OTC Volume 020133. The results of this study were later reputed as being due to oral ingestion of the drug by the animals, nevertheless, brain toxicity was reported (Ref. 1). A study done in dogs, OTC Volumes 020181 to 020183, was reported to the Panel as producing negative results but showed some questionable liver changes. In this study there was a positive control dosed with hexachlorophene showing brain damage (Ref. 1).

The carcinogenic, mutagenic and teratogenic potentials of this agent, which is absorbed through the skin, have not been adequately studied.

b. *Microbiology and clinical efficacy.* From the standpoint of effectiveness, laboratory studies revealed that tribromsalan is not a unique antimicrobial agent. It has antimicrobial activity against gram positive organisms, particularly against *Staphylococcus aureus* and other staphylococcal species, but not against fungi such as *Candida albicans,* gram negative organisms such as *Pseudomonas* species or coliformtype microorganisms. Furthermore, evaluation of several clinical studies utilizing tribromsalan-containing soaps including data by Leonard (Ref. 2), Duncan et al. (Ref. 3) and Wheatly et al. (Ref. 4) revealed no unequivocal or significant prophylactic effect of tribromsalan-containing preparations against superficial skin infections. The reader is referred to the extensive discussion of the efficacy and clinical tests of antimicrobial soaps under the Effectiveness of Antimicrobial Bar Soaps. A therapeutic effect of tribromsalan (as one of three ingredients) against erythrasma, a skin infection, was reported by Kooistra (Ref. 5), Dodge et al. (Ref. 6) and Rosenberg and Allen (Ref. 7). This finding of effectiveness against cutaneous *Corynebacterium minutissimum* infections cannot be taken to support OTC claims for effectiveness against more serious clinical pyogenic infections caused by other organisms. See also discussion under Erythrasma.

The use of a soap containing 1 percent tribromsalan in combination with 1 percent triclosan was reported in a study (Ref. 8) in which leukemic patients were bathed to reduce the total microbial flora on the skin. The authors reported that 60 percent of the 186 strains of organisms initially cultured were eliminated within two weeks after bathing with the test soap. The patients were not only in a highly artificial "life island unit" but they also received a number of both topical and systemic antibiotics at the same time as the soap was tested. The results could hardly be projected to conclude that tribromsalan is efficacious in the prevention of infection or the elimination of potential pathogens from the skin. This study is also discussed in detail in the Panel's statement on triclosan.

The authors of the study (Ref. 8) themselves suggest that their skin sampling techniques were only semi-quantitative and that they estimate only 40–60 percent of the organisms were recovered with their moist swab technique. The cultural techniques were not optimal for the isolation of the variety of organisms present on the skin. The Panel cannot support the conclusions that tribromalan is effective in the prophylaxis of skin infection from the data presented in this study. In fact in a subsequent publication (Ref. 9), these same authors describe another study of this type and conclude that although 76 percent of aerobic bacteria were eliminated by cleansing with a soap containing a combination of triclosan, and tribromsalan, strains of potential pathogens such as *Enterobacter* species, a *Klebsiella* species, *Proteus* species and *P. aeruginosa* persisted. Thirty-three percent of the patients had persistent pathogenic bacteria and 40 percent had persistent fungi. Despite intensive systemic and topical antibiotic therapy and washing with an antimicrobial soap as a protective measure, the organisms persisting were those most likely to cause fatal infections in these serious ill patients.

In the judgment of the Panel, clinical effectiveness in the prophylaxis and treatment of superficial pyogenic infections of the skin has not been established. Deodorant effectiveness for tribromsalan has been demonstrated in the reports reviewed, but safer, alternative agents for the reduction of body odor exist (see discussion of toxicity for triclosan, triclocarban and cloflucarban included elsewhere in this document).

c. *Photosensitivity—1—Historical review.* Shortly after the first use in Europe of halogenated salicylanides (e.g. tetrachlorsalicylanilide) as antibacterial agents in soaps they were shown to cause a severe photodermatitis and had to be removed from the market (Ref. 10 and 11). A related chemical, bithionol, caused the same type of light-induced dermatitis (Ref. 12) and also was removed from products for human use.

In 1965 the related tribromosalicylanilide (tribromsalan, TBS) was incorporated into bar soaps in the United States and product related cases of photodermatitis began to appear (Ref. 13–17). It is important to note that the photosensitization reaction occurs with tribromsalan at the level formulated in bar soaps for consumer use. In 1967 and 1968, patients with tribromsalan photodermatitis were being reported throughout the United States (Wisconsin, Ref. 14; New York, Ref. 17, 18; Florida, Ref. 19, 20; Minnesota, Ref. 21; and California, Ref. 22) as well as France (Ref. 23), Denmark (Ref. 24, 25), Canada (Ref. 26), Australia (Ref. 27), and Japan (Ref. 28). Wherever the tribromsalan soap was used photodermatitis appeared. The voluminous literature was summarized in a book in 1972 (Ref. 29) and is also reviewed in OTC Volume 020056 (Ref. 1).

Because photodermatitis is not an officially reportable disease accurate figures on its incidence are not available. As "soap photodermatitis" became well known to practicing dermatologists and other physicians (1968–1972), there was less need and less likelihood of such patients being referred to special centers studying photodermatitis and recording cases. As a result because they are recognized, fewer cases were likely to be seen and recorded by the photobiologists. In 1972, the second most popular bar soap in the United States removed tribromsalan from its formula and thereafter only several less widely distributed brands continued to include it in their products. Tribromsalan was never included as an active ingredient in the most widely sold antimicrobial bar. The Panel believes that the number of cases reported by dermatologists in photobiology centers has decreased during 1973 as a result of these factors.

The above reasons may account for the impression that tribromsalan photodermatitis is less common than it was. The Panel, however, wanted to know if the disease had disappeared or if it was still occurring. Therefore, in 1972–73, they questioned 8 dermatologists in different parts of the United States who had studied or published on this disease. Although most agreed that the incidence was declining in their practices, 6 of the 8 reported that it was still a problem and that new cases were occurring (Ref. 1 in OTC Volume 020164).

Photosensitization has been reported with hexachlorophene, triclocarban and cloflucarban (Ref. 28). However, these reports in the literature document the existence of only a very few, rare cases. These ingredients have not caused persistent light reactions as far as is known. Only a few case reports exist in spite of the widespread use of these ingredients compared to the many reported cases of tribromsalan photosensitization.

2. *Clinical appearance and nature of the problem.* Photocontact dermatitis appears as an inflammation of the areas of the skin exposed to light. It begins as redness with itching and burning usually on the face and then hands, arms, and neck. The eruptions are frequently limited to the exposed portions of the hands, arms and face and characteristically spare the upper eyelid and submental area. However, a patchy eczematous rash on the trunk and other covered areas is not uncommon. Many cases proceed to get worse so that the red areas develop blisters, scabs and pus. If the process continues, the skin thickens with a furrowed pebbly surface and the patient is chronically incapacitated. In most cases whether acute or chronic, the terrible itching and burning disturb sleep, and the unsightly appearance prevents the patients from working.

In most victims if the photosensitizing chemical such as tribromsalan is discovered and completely avoided, the dermatitis will clear in a few weeks. However, in some patients, the reaction con-

tinues without apparent further exposure to the chemical. A persistent light reactor is an individual, who, though not exposed to any further dose of the sensitizing chemical, continues to have typical and frequently severe symptoms of photocontact dermatitis for months or years when exposed to light. Such a persistent light reactor is severely disabled and frequently unable to earn a livelihood. Ordinary daylight alone is sufficient to cause swelling of the face and exposed skin. In the more chronic cases, some of these patients develop markedly thickened skin and ears which may resemble the clinical appearance of leprosy. Such patients are "dermatological cripples" and are confined to dark rooms and the indoors during all daylight hours and are unable to work. This condition may continue for months or even years. To trigger such a reaction with a product containing tribromsalan is to cause a disaster to an unsuspecting user of an unnecessary product. Persistent light reactions as well as photocontact dermatitis have been reported after using soaps containing tribromsalan from all parts of the United States (Ref. 29).

d. *Animal models.* Attempts to develop an animal assay for photocontact sensitizers have not been altogether successful. On the basis of their animal model studies, Vinson and Borselli (Ref. 30) claimed that tribromsalan "is neither a photosensitizer nor a cross photosensitizer". They reiterated this view in 1969 (Ref. 31). However, Harber et al. (Ref. 18), with tribromsalan, produced contact photosensitivity in 7 animals; combined with contact sensitivity, in 1/21 animals. Using tetrachlorosalicylanilide on 65 guinea pigs they induced contact photosensitivity alone in 20 animals, contact sensitivity alone in four animals and both types of reaction in a further twelve guinea pigs. Thus Harber et al. (Ref. 18) found in animals and in man that tribromsalan is a photosensitizer and a cross-photosensitizer and suggest that the disagreement of their results with those of Vinson and Borselli may be due to a variety of experimental differences.

e. *Discussion.* In addition to the problems of efficacy and safety enumerated above, an overriding consideration for the Panel was the recognized fact that tribromsalan can lead to severe and persistent light reactions in sensitized individuals. The question therefore, was whether its use should be allowed in the face of a benefit limited to deodorant activity.

Osmundsen (Ref. 24), in the summer of 1967, diagnosed 39 cases of photocontact dermatitis caused by a soap containing tribromsalan and 27 additional cases (Ref. 32) later that year. Thus, in one year contact photodermatitis caused by tribromosalicylanilide has been diagnosed in 66 patients (11 females and 55 males) in Copenhagen. Photo-cross-reaction to different halogenated salicylanilides was also found, indicating the 4'-bromosalicylanilide elicited positive simple patch tests in 11 out of 20 patients. It was suggested by Osmundsen that the 4'-position and the halogen substitution was a key point in the sensitization process.

It was also shown by Osmundsen in 1968 (Ref. 24) that "pure" tribromsalan may elicit a positive photopatch test in a concentration as low as 0.0001 percent. It seemed probable to him that tribromsalan, rather than an impurity, is the photosensitizer. Harber et al. in 1966 (Ref. 17) addressed themselves to the possibility that tribromsalan impurities, not tribromsalan itself, were responsible for the photosensitizing reaction. They photopatch tested a tribromsalan photosensitive patient with a more than 99 percent "pure" preparation of tribromsalan (0.1 percent in petrolatum) and elicited a 3+ reaction. This reaction was of the same intensity as the one produced in the same patient with less "pure" tribromsalan preparations obtained from other sources. These authors concluded that it was highly unlikely that the photocontact responses were due to a contaminant. Ison and Tucker (Ref. 19) published similar results.

According to the manufacturer, the offending soap marketed in Copenhagen contained 2 percent tribromsalan.

A recently published book, "Soap Photodermatitis," by Herman and Sams (Ref. 29) deals exclusively with photodermatitis caused by antimicrobial ingredients especially salicylanilides in soap. This book, other articles, and additional conversations between the Panel and Drs. Herman and Sams leave no doubt as to the authors' view that tribromsalan causes photocontact dermatitis and is a primary photosensitizer (Ref. 29 and 33).

One manufacturer has claimed that the contamination of tribromsalan with the known photosensitizer, dibromsalan is the cause of photosensitization, and that with the increasing purity of tribromsalan the incidence of photosensitization has decreased and will disappear. The Panel accepts the fact that the incidence has decreased (see discussion above). However, it definitely has not disappeared for cases are still reported (OTC Volume 020164, Ref. 1). Tribromsalan can also cause a photosensitization reaction in individuals who have been primarily sensitized with other salicylanilides. To the individual sensitized, it makes little difference what the compound causing the original sensitization was. Furthermore hard surface cleansers still (May, 1974) contain dibromsalan as well as tribromsalan so that sources of photosensitizing chemicals exist today in other than bar soap products.

The Panel's serious concern about tribromsalan comes from reports that patients are still appearing in the United States who have disabling photodermatitis which has been caused by soaps containing the current purified tribromsalan material. Photopatch testing of these patients has confirmed the clinical diagnosis and identification of tribromsalan as the cause of their dermatitis. Potentially confusing photosensitizers, such as TCSA, are no longer used in photopatch testing and the Panel believes that the current photopatch tests accurately incriminate tribromsalan as the cause of the dermatitis.

f. *Conclusion and summary.* The Panel believes that the benefit from using tribromsalan containing soaps is insignificant when faced with the risk. Thus, even if the number of persistent light reactors is small in relation to the amount of tribromsalan used, when there is so little benefit, it is unjustified to subject even a few individuals to such a risk. In addition, the Panel was unable to resolve the inconsistencies in the reported toxicity data. For this reason, but especially because of the photodermatitis, it was the Panel's judgment that it would be safer for society not to have this drug sold over the counter.

From their review of the data concerning photosensitization, the Panel believes that the evidence is clear that both dibromsalans (3, 5 dibromosalicylanilide and 4', 5 dibromosalicylanilide) and tetrachlorosalicylanilide (TCSA, 3, 3', 4', 5 tetrachlorosalicylanilide) are more potent photosensitizers than tribromsalan. Therefore, regardless of the fact that these ingredients were not submitted to the Panel for review, the Panel concludes that the Food and Drug Administration should move to also ban completely the use of dibromsalan and tetrachlorosalicylanilide in drugs and cosmetics.

Therefore, after a thorough review of all of the available data, the Panel recommends to the Commissioner that tribromsalan be considered not safe for general use as an OTC antimicrobial ingredient in man and that the Food and Drug Administration take action to ban tribromsalan, dibromsalan, and tetrachlorosalicylanilide from OTC antimicrobial products. The Panel concludes that these salicylanilides should not be implemented in a manner similar to other Category II ingredients but should be handled more expeditiously by publication of a separate FEDERAL REGISTER notice in a manner similar to that used for hexachlorophene.

Furthermore, they also recommend that the Food and Drug Administration inform the appropriate regulatory agencies of the Panel's recommendations that dibromsalans (4', 5 dibromosalicylanilide and 3, 5 dibromosalicyanilide) and 3, 3', 4', 5-tetrachlorosalicylanilide be removed from drugs and cosmetics and also inform them of the risk associated with the marketing of these ingredients in hard surface cleansers and disinfectants.

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FLUOROSALAN

3. The OTC Antimicrobial I Panel has reviewed the submission (Ref. 1) concerning the safety and effectiveness of fluorosalan (fluorophene, 3, 5-dibromo-3'-trifluoromethyl salicylanilide) and is of the opinion that fluorosalan cannot be generally regarded as safe for use as an OTC antimicrobial agent in man. The data submitted for this ingredient were minimal. The similarity of this molecule to tribromsalan requires that sufficient data be submitted to properly assess the risk-benefit ratio from the use of this chemical as an antimicrobial. Included in the reasons for this opinion are the following.

The chemical, even in pure form, may, as a dibromo-substituted salicylanilide, possess potential for photosensitization in man, and its use could result in a serious dermatological condition known as persistent light reaction (see discussion of tribromsalan). Evidence demonstrating that phototoxicity and/or photosensitivity would not result from the use of fluorosalan has not been submitted.

The absorption, tissue distribution, route(s) of metabolism and excretion, and blood levels attained after topical application are not available.

Information about the relationship between blood levels and toxicity is not available.

Studies on the carcinogenicity, mutagenicity, teratogenicity and reproductive effects are not available.

In addition, controlled studies demonstrating clinical effectiveness are not available.

The Panel agreed that any use of this ingredient should be under a Notice of Claimed Investigational Exemption for a New Drug and a New Drug Application until further data are collected.

REFERENCE

(1) OTC Volume 020050.

PHENOL GREATER THAN 1.5 PERCENT AQUEOUS/ALCOHOLIC SOLUTION

4. The Panel reviewed a number of products containing phenol in a variety of vehicles. There was a paucity of data submitted delineating the influence of vehicle on the effectiveness or toxicity of phenol. A search of the literature was productive in preparing this statement relating the concentration of phenol in aqueous or alcoholic vehicles to toxicity.

It is the recommendation of the Panel that Phenol concentrations greater than 1.5 percent in aqueous or alcoholic vehicles be placed into Category II.

The data supporting this decision may be found in standard reference texts such as Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ref. 1), AMA Drug Evaluations (Ref. 2), Patty's Industrial Hygiene and Toxicology (Ref. 3) and in Deichmann's review of phenol (Ref. 4).

Basically, these references document the toxicity of phenol when applied topically. For example, the authors have noted that a 2 percent ointment resulted in blood levels of 0.8 mg. of free phenol or 2.3 mg. of conjugated phenol per 100 ml. of blood. It should be noted that 30 mg. of free and 1 mg. of conjugate are fatal concentrations. One to 5 percent phenol applied as a dressing or compress has caused gangrene.

It has also been recorded that 2 percent and higher concentrations of phenol in aqueous vehicles have caused serious hazards, including gangrene, anesthesia, mummification and even, coma. Phenol is more soluble in alcohol than in water and would penetrate to deeper layers of the skin producing severe burns and might be systemically absorbed in higher concentrations. Therefore, for these reasons phenol in concentrations greater than 1.5 percent is placed in Category II.

The acute systemic toxic effects of phenol in man and animals is observed primarily as an effect on the central nervous system. Sudden physical collapse has been observed in man after systemic exposure associated with other effects such as myocardial depression and marked blood pressure fall. There may also be marked dyspnea and a decrease in body temperature (Ref. 3). These systemic effects are related to the amount of free phenol in the blood. A blood level of 30 mg. of free phenol per 100 ml. of blood can be fatal and death is usually the result of respiratory failure (Ref. 3).

Chronic poisoning in man results in digestive disturbances, such as vomiting, difficulty in swallowing, diarrhea, and anorexia. Nervous disorders, such as headache, fainting, vertigo, and mental disturbances also occur. In severe cases, sometimes fatal, there may be extensive damage to the kidneys and liver. Most of the reported cases of chronic poisoning have resulted from ingestion or inhalation (Ref. 3). However, it is possible that repeated topical application over large surfaces of the body could lead to the systemic effects described above.

After absorption, phenol is excreted in the free form in the urine or is conjugated in the liver to the glucuronide or sulfate, prior to excretion in the urine. Some is expired in the air. In the rabbit, after a single oral dose, 23 percent was oxidized in the body to carbon dioxide and water plus pyrocatechol and hydro-

quinone. Of the 72 percent excreted in the urine, 48 percent was excreted as the free phenol and 52 percent as the conjugates. Only 1 percent of the total administered dose was excreted in the feces (Ref. 3). In addition, Boutwell and Bosch (Ref. 5) have reported that phenol is a cocarcinogen in animals.

With local dermal application of high concentrations, a pellicle of denatured protein is formed which may turn red and slough, leaving a brown stain. Prolonged contact of phenol with the skin, resulting in deep penetration of the skin, can produce gangrene and necrosis (Ref. 1 and 3). Ochronosis (darkening of the tissue) can also result from prolonged dermal contact (Ref. 3). If applied to mucous membranes or swallowed, phenol can cause swelling, corrosion, necrosis and hemorrhages of the mucous membranes of the throat or gastrointestinal tract.

In the past, preparations of 1 to 5 percent phenol in aqueous solutions have been used with dressing and compresses. This has resulted in gangrene, primarily when applied to fingers and toes (Ref. 3). Preparations containing 1 to 2 percent phenol have been formulated frequently in salves or ointments and with vegetable oil or calamine lotion for antipruritic effects. The use of 2 percent phenol ointment has resulted as reported above in blood levels of 0.8 mg. of free phenol and 2.3 mg. of conjugated phenol per 100 ml. blood (Ref. 3). Blood levels of phenol attained after application of phenol in liquid preparation have not been presented.

The use of low concentrations of phenol (1 to 2 percent) in ointments, lotions, salves or solutions can cause toxicity leading to severe incidence of gangrene with prolonged contact and/or occlusion of the treated area (Ref. 3). Rat studies have shown that a 1.78 percent phenol-liquid petrolatum solution will cause gangrene and necrosis after 8 hours of exposure in 2 to 3 days. A 4.15 percent aqueous phenol solution caused gangrene in the same period of time (Ref. 6). The use of oil in the formulation may enhance the toxicity.

Camphor also has been used in formulations containing phenol. Camphor may in fact retard the absorption and availability of phenol from the solution. However, the local toxicity of phenol in a camphor-containing preparation depends upon the aqueous/phenol phase resulting from the presence of tissue fluids or perspiration (Ref. 3). Camphor, if present with phenol, will "hold" the phenol, as is evidenced by the study which demonstrated that, while 60 percent of the phenol in a saturated solution of liquid petrolatum is in the aqueous phase, only 22 percent of the phenol in a 4.6 percent phenol 10 percent camphor combination in liquid petrolatum is in the aqueous phase. When the camphor concentration was raised to 21 percent, only 10 percent of the phenol was in an aqueous phase (Ref. 6). The presence of camphor also retards the absorption of phenol afer topical application. A 1-hour exposure of the rat tail to a 4.8 percent aqueous phenol solution resulted in the absorption of 71 mg. of phenol; whereas, the presence of 10.9 percent camphor combined with 4.5 percent phenol resulted in the absorption of only 16 mg. phenol (Ref. 7).

No data have been submitted with regard to absorption of phenol from mucous membranes, although this is a route of application described in the labeling submitted for some products.

Information citing the local toxicity and absorption of phenol, has been reported by Bass and Werch (Ref. 8), Conning and Hayes (Ref. 9), Deichmann (Ref. 4), Freeman et al. (Ref. 10), Mannheimer and Adriani (Ref. 11), Ruedemann (Ref. 12), and Woolley (Ref. 13).

The Panel concludes that phenol in concentrations greater than 1.5 percent in aqueous or alcoholic vehicles is not safe for general use as an OTC antimicrobial agent in man.

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TINCTURE OF IODINE

5. The Panel considers the use of elemental iodine in aqueous or hydro-alcoholic solution unsafe for general use on the skin other than as a Patient Pre-Operative Skin Preparation. It has been well documented (Ref. 1, 2 and 3) that iodine is irritating to broken skin and delays wound healing, especially when occlusive dressings are applied.

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CLOFLUCARBAN

6. The Panel has determined that it is appropriate to include cloflucarban in Category II for the following product uses: Patient Pre-operative Skin Preparation, Skin Antiseptic, Skin Wound Cleanser, Skin Wound Protectant and Surgical Hand Scrub. Cloflucarban is classified in Category III as a Skin Wound Cleanser when formulated in a bar soap to be used with water.

The Panel included cloflucarban in Category II for these uses since no data were presented to support its use for the product categories identified. This statement is not to be construed to mean that the ingredient may not be shown to be safe and effective for the product categories listed.

The Panel's concern is that consumer use of the ingredient may occur before adequate research is conducted.

TRICLOCARBAN

7. The Panel has determined that it is appropriate to include triclocarban in Category II for the following product uses: Patient Pre-operative Skin Preparation, Skin Antiseptic, Skin Wound Cleanser, Skin Wound Protectant and Surgical Hand Scrub. Triclocarban is classified in Category III as a Skin Wound Cleanser when formulated in a bar soap to be used with water.

The panel included triclocarban in Category II for these uses since no data were presented to support its use for the product categories identified. This statement is not to be construed to mean that the ingredient may not be shown to be safe and effective for the product categories listed.

The Panel's concern is that consumer use of the ingredient may occur before adequate research is conducted.

TRICLOSAN

8. The Panel recognizes that a Health-Care Personnel Handwash, Patient Pre-Operative Skin Preparation, or a Surgical Hand Scrub are designed primarily for extensive use in the hospital or other closed environment. The Panel has therefore included these uses in Category II for triclosan.

The Panel has concluded (see discussion in Category III for Triclosan) that formulations containing this ingredient should not be used in these environments because of possible increased one-way environmental pressures toward gram negative (especially *Pseudomonas*) infections. In the event that data are submitted to show that the Panel's conclusion is not justified, consideration should be given for inclusion of the ingredient in these product categories.

COMBINATION ANTIMICROBIAL PRODUCTS

The Panel, in its deliberations, received two submissions on antimicrobial

bar soaps containing a combination of active ingredients, and one of these containing triclocarban and cloflucarban was classified in Category III. The other soap combination contained tribromsalan and triclosan and has been placed in Category II. Information on the safety and effectiveness of other combinations of ingredients were not received. Therefore, for lack of data they are not generally recognized as safe and/or effective. Conditions possibly exist where the benefit to risk ratio is such that their use may be of value, if not necessity. However, such combination antimicrobial agents should not be available for over the counter use until sufficient safety and efficacy data are submitted.

The level of each antimicrobial ingredient in the combination must make a contribution to the claimed effect for the product. The total amount of individual antimicrobial ingredients, in combination, should result in an effect that is at least equal to that achieved when any one of the individual ingredients is used alone at the same total concentration without significantly reducing safety. In some instances the Panel has established maximum dose levels of an antimicrobial when used alone. If such antimicrobials are placed in combinations no individual antimicrobial in the combination may exceed the dose level approved by the Panel. The Panel feels that a rational combination of antimicrobials should have one of the following purposes: Expansion of the microbial spectrum, reduction of the toxicity of one or both of the ingredients, or result in a synergistic effect.

Furthermore, when two or more ingredients are combined, toxicity data must be available to show that neither the metabolism, excretion or target organ toxicity are enhanced, or are synergistically affected by the combination, for example, through the metabolism or excretion of one of the ingredients.

The Panel feels that the safety of combinations is sufficiently important to recommend that when such ingredients are used in combinations in antimicrobial soaps, an approved New Drug Application should be obtained prior to marketing. At a later date, when sufficient safety and effectiveness data warrant it, combinations of these ingredients may be placed in Category I.

LABELING

The Panel concludes that there are insufficient data to support certain labeling terms or claims. Because no data are available these terms and claims are misleading to the consumer and result in misbranding of the product. The claims that shall not be allowed are:

A. Speeds, promotes or aids healing (or any similar statement).
B. Sanitizes the skin or wound.
C. Sterilizes the skin or wound.
D. Ensures bacterially clean skin.
E. Disinfects the skin or wound.
F. Heals (wounds).
G. Controls infection.

III. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that the conditions specified in Category III be made effective 1 year after publication of the final monograph in the FEDERAL REGISTER.

ACTIVE INGREDIENTS

A. The active ingredients for which the available data are insufficient to permit final classification for use in "antimicrobial soaps" are:

1. Cloflucarban.
2. Para-chloro-meta-xylenol.
3. 1.5 percent Phenol or less—aqueous/alcoholic.
4. Triclocarban.
5. Triclosan.

B. The active ingredients for which the available data are insufficient to permit final classification for use in a "health-care personnel handwash" are:

1. Benzalkonium chloride.
2. Benzethonium chloride.
3. Cloflucarban.
4. Hexylresorcinol.
5. Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
6. Methyl-benzethonium chloride.
7. Nonylphenoxypoly (ethyleneoxy) ethanol-iodine.
8. Para-chloro-meta-xylenol.
9. 1.5 percent Phenol or less aqueous/alcoholic.
10. Poloxamer-iodine complex.
11. Povidone-iodine complex.
12. Triclorcarban.
13. Undecoylium chloride-iodine complex.

C. The active ingredients for which the available data are insufficient to permit final classification for use in a Patient "pre-operative skin preparation" are:

1. Benzalkonium chloride.
2. Benzethonium chloride.
3. Hexylresorcinol.
4. Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
5. Methylbenzethonium chloride.
6. Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
7. Para-chloro-meta-xylenol.
8. 1.5 percent Phenol or less—aqueous/alcoholic.
9. Poloxamer-iodine complex.
10. Providone-iodine complex.
11. Undecoylium-chloride complex.

D. The active ingredients for which the available data are insufficient to permit final classification for use in a "skin antiseptic" are:

1. Benzalkonium chlorida.
2. Benzethonium chloride.
3. Hexylresorcinol.
4. Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
5. Methyl-benzethonium chloride.
6. Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine.
7. Para-chloro-meta-xylenol.
8. 1.5 percent Phenol or less aqueous/alcoholic.
9. Poloxamer-iodine complex.
10. Povidone-iodine complex.
11. Triclosan.
12. Triple Dye.
13. Undecoylium chloride-iodine complex.

E. The active ingredients for which the available data are insufficient to permit final classification for use in a "skin wound cleanser" are:

1. Iodine complexed with phosphate ester of alkylaryloxy polyethlene glycol.
2. Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine complex.
3. Para-chloro-meta-xylenol.
4. 1.5 percent Phenol or less—aqueous/alcoholic.
5. Poloxamer—Iodine complex.
6. Povidone—Iodine complex.
7. Triclosan.
8. Undecoylium chloride—Iodine complex.

F. The active ingredients for which the available data are insufficient to permit final classification for use in a "skin wound protectant" are:

1. Benzalkonium chloride.
2. Benzethonium chloride.
3. Hexylresorcinol.
4. Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
5. Methyl-benzethonium chloride.
6. Nonyl phenoxypoly (ethyleneoxy) ethanol iodine.
7. Para-chloro-meta-xylenol.
8. 1.5 percent Phenol or less—aqueous/alcoholic.
9. Poloxamer-iodine complex.
10. Povidone-iodine complex.
11. Triclosan.
12. Undecoylium chloride-iodine complex.

G. The active ingredients for which the available data are insufficient to permit final classification for use in a "surgical hand scrub" are:

1. Benzalkonium chloride.
2. Benzethonium chloride.
3. Hexylresorcinol.
4. Iodine complexed with phosphate ester of alkylaryloxy polyethylene glycol.
5. Methyl-benzethonium chloride.
6. Nonyl-phenoxypoly (ethyleneoxy) ethanol-iodine.
7. Para-chloro-meta-xylenol.
8. 1.5 percent Phenol or less—aqueous/alcoholic.
9. Poloxamer-iodine complex.
10. Povidone-iodine complex.
11. Undecoylium-chloride iodine complex.

GENERAL COMMENT APPLICABLE TO ALL INGREDIENTS IN CATEGORY III

The Panel has concluded that adequate and controlled studies are not available at this time to permit the final classification of the active ingredients listed above.

The recent hexachlorophene experience has made apparent to the scientific community that toxic levels of antimicrobial chemicals applied to the skin can be absorbed into the body. The greatest lack of substantial data is in the following areas: Retention and/or substantivity, absorption, blood level, organ distribution, possible tissue depoting, metabolism, and excretion. In many cases analytic procedures for the determination of active ingredients and/or metabolites in tissues and secretions have been developed only recently.

A major emphasis in the past has been on the collection of data to support the effectiveness of antimicrobial products applied to the skin. These data have often been reported as "percent reduction" of the microbial flora on the hands. Such data reflect the reduction of the normal skin microbial flora or of that acquired by contact with the environment. More sophisticated procedures for the analysis of microbial reduction data which involve techniques for dealing with initial high variation in microorganism counts, and the correlation of reduction in microbial flora with prophylaxis of infection, are required. In addition to numerical reduction, data must be accu-

mulated on the effect of antimicrobials on the balance of the normal microbial flora, including the diptheroids. These aspects of effectiveness data are essential before risk-benefit judgments can be reasonably made.

The Panel has determined that Category III ingredients may be permitted to remain in use until 1 year after publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such product conducts tests and studies to satisfy the questions raised by the Panel.

The Panel recognizes the complexity of this report and the difficulties that may be encountered in interpreting the required studies necessary for an ingredient included in Category III. The following sections of this report should be collectively considered before undertaking any proposed studies: (1) The historical discussion of the product category in the Panel's comments concerning effectiveness in the use of antimicrobial products, (2) the guidelines for testing, (3) the product category definition and subsequent discussion and (4) the specific statement for the ingredient to be tested.

TRICLOCARBAN

1. The OTC Antimicrobial I Panel has determined that the only permitted use of triclocarban (TCC, 3, 4, 4'-trichlorocarbanilide) at the present time should be as an antimicrobial ingredient in bar soap. The manufacturer gave assurances to the Panel that this was the only use for which the chemical is being sold at this time. However, the Panel also recognizes that the manufacturer's patent on triclocarban expires within two years, and expressed their concern about the possible future proliferation of its use in various OTC products, thereby increasing the possible total body burden.

The Panel reviewed the available effectiveness and safety data on triclocarban and concludes that adequate data are not yet available to permit final classification of triclocarban for use in bar soap. Other applications were not considered. The available evidence does not indicate that the use of triclocarban in bar soaps presents any known hazard to the general public. For example, the LD_{50} of triclocarban intraperitoneally in rats is reported to be in excess of 2,000 mg/kg compared to 6.25 mg/kg for hexachlorophene. See OTC Volume 020139 (Ref. 1). Based on blood level data, which is not complete at this time, triclocarban does not appear to be as toxic as hexachlorophene. Therefore, the Panel recommends to the Commissioner that triclocarban use in bar soaps be permitted at a concentration not to exceed 1.5 percent for a period of 1 year following publication of the final monograph in order to allow interested parties time to conduct the necessary research to correct the deficiencies indicated below.

A primary area of concern is the data defining the target organ for toxicity. At high blood levels of triclocarban, (in excess of 200 ppm TCC/TCC metabolite), the apparent target organ in rats is the testicles. In the opinion of the Panel, the data relating the blood level of triclocarban to testicular damage are still not definitive. For example, one set of data in OTC Volume 020189 (Ref. 1) estimated that blood concentrations of 50 to 70 ppm TCC/TCC metabolite caused pathological changes in the testicles of test animals. More recent data from a feeding study at 400 mg/Kg/day in OTC Volume 020165 (Ref. 1) suggests that 200 ppm TCC/TCC metabolite in the blood was an "effect level" and that a dose of 200 mg/Kg/day giving a blood concentration of 100 ppm TCC/TCC metabolite was a "no effect" level. Still other data in the OTC Volume 020139 (Ref. 1) suggested testicular lesions at oral doses lower than those which resulted in the "no effect" blood levels mentioned above (100 ppm). In view of these conflicting data regarding blood levels and ensuing testicular damage, the Panel regards this as an area of significant deficiency in the data. Adequate data relating blood level to target organ toxicity and "no-effect" levels will be required.

Maibach (Ref. 2) has shown that triclocarban may be absorbed through human skin after topical application. In this one study, 14 percent of the dose applied in acetone solution was absorbed. Elimination of triclocarban after topical application was slower than after ingestion, suggesting possible accumulation in the body. However, the adequacy of analytical methods for the detection of triclocarban and all its metabolites is still questionable, and is made more difficult by the very low levels which must be detected in blood or tissue. Based on some theoretical and some actual data, calculations of potential blood levels in man were made. It is the conclusion of the Panel that, until definitive data are accumulated to show blood levels in man from actual use, the concentration of triclocarban in bar soaps should be limited to 1.5 percent. The calculation which led to this conclusion follows, but it should be emphasized that the cause of testicular lesions has not yet been determined to be triclocarban (parent compound), TCC-metabolite or the combination, (TCC/TCC metabolite). Additionally, inadequate data on rate of elimination were a factor in setting this 1.5 percent limit. The following calculations make certain assumptions which may prove to be inaccurate once adequate data are obtained:

1. Assume that a bar soap contains 2 percent triclocarban and that an average bath uses 7.0 gm of soap. The total available triclocarban, if instantaneous absorption occurred would be 140 mg triclocarban.

2. Assume 2 percent of this 140 mg triclocarban remains on the skin as a substantive agent. This retention presents to the body a total of 2.8 mg of triclocarban for absorption.

3. Assume that 14 percent of the available 2.8 mg were absorbed, as shown by Maibach (Ref. 2). This would allow 0.392 mg of triclocarban to be absorbed from a single bath.

4. Assume that an average size human has 5,000 ml of blood, and that 0.392 mg of triclocarban were instantaneously absorbed. The concentration of triclocarban in the blood would be approximately 0.1 ppm. Considering that some part of the population takes two baths per day, and assuming that the total triclocarban to which the individual was exposed accumulated during that day, the blood level would be 0.2 ppm. Data from the manufacturer indicate that triclocarban as the parent compound disappears from the blood within minutes. The exact mechanism(s) of absorption and elimination is not yet clear.

5. If we take the most recent data submission to the Panel indicating that 100 ppm total TCC (TCC/TCC metabolite) in the blood is the "no-effect" level, then a safety factor could be calculated as follows:

$$\frac{100\text{ ppm}}{0.1\text{ ppm}} = 1{,}000\text{-fold safety factor (single bath)}$$

or

$$\frac{100\text{ ppm}}{0.2\text{ ppm}} = 500\text{-fold safety factor (2 baths per day)}$$

Since these safety factors have been calculated from blood levels, they would certainly be reasonable safety factors for allowing the continued use of triclocarban in bar soaps. However, it should be stressed that several assumptions have been made in deriving these calculations and the Panel urges that definitive data to clarify these assumptions be generated. For example, assumptions were made as to substantivity that 14 percent of applied TCC is absorbed, that instantaneous absorption results in certain blood levels, that accumulation does not occur, that skin condition did not influence blood levels, and that metabolism was an uncalculated factor.

The Panel strongly recommends that adequate research include studies to determine the substantivity of triclocarban over a period of time and in various areas of the body, the amount of triclocarban deposited on the skin from a single bath, and the blood levels attained in individuals in various age groups and with various skin conditions following use of soap containing triclocarban.

Unconfirmed data suggesting additional toxic effects were submitted to the Panel and it is felt that clarification of these data is necessary. For example, brain and splenic changes were noted by two pathologists in one study reported in OTC Volume 020139 (Ref. 1), while other data indicated that no such tissue changes occurred. The Panel believes that these conflicting data need further clarification even though the initially reported toxic effects could not be confirmed in further, similar experiments. The suggestion of brain and splenic changes is of such importance that it cannot be ignored. It is conceded that the animal strain used in the initial experiment was unusual (Cox strain of rats). Definitive research in at least two animal species at exaggerated dose levels is recommended in order to specifically answer the questions about potential brain or splenic changes. Where changes

are seen, concomitant blood levels of triclocarban should be investigated.

It is the opinion of the Panel that adequate studies have been submitted (Ref. 1) to indicate that triclocarban has no real potential for the induction of carcinogenesis, mutagenesis, or teratogenesis. However, the data submission in OTC Volume 020165 (Ref. 1) suggested that with triclocarban orally administered in rats, there was a decrease in implantation sites and a decrease in the number of offspring at high dose levels of triclocarban (1,000 ppm) in the diet. In fact, the results of these studies in OTC Volumes 020165 and 020189 (Ref. 1) originally directed attention to testicular effect. The Panel recommends that adequate research be conducted to define more clearly the implications of the data.

A major route of elimination of triclocarban from the body is reported to be via conjugation to the glucuronide in the liver. This mechanism is deficient in young animals and human infants. The Panel felt that inadequate data concerning elimination and toxicity in young animals were submitted, and recommends that adequate research in young animals with blocked formation or unavailable glucuronide systems be conducted in order to define the toxicity potential for human infants who may be bathed in a soap containing triclocarban.

Since the liver is considered the major organ for conjugation, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

Therefore, the Panel recommends that unless such studies as described above are conducted within 1 year following publication of the final monograph in the FEDERAL REGISTER, this ingredient should be restricted from use in infants. The label for the preparation containing the ingredient would state: "Not to be used on infants under 6 months of age." The literature sources documenting the impairment of glucuronide capacity in infants are listed separately under, "Glucuronide Capacity in Infants" (Refs. 1 through 7).

The Panel recognizes the triclocarban will decompose at elevated temperatures in aqueous solution to yield chloroanilines. There are reported incidences of methemoglobinemia resulting from high temperature decomposition by triclocarban by Johnson et al. (Ref. 3). Therefore, soaps or soap products containing triclocarban should not be heated and subsequently used in or on the human body. Additionally, since chloroanilines do have a potential for inducing methemoglobinemia at higher blood levels, the chloroaniline content in bar soaps containing triclocarban should be monitored to limit it to less than 100 ppm. (See the data in OTC Volume 020127, page 15, line 22 (Ref. 1). The Panel felt that adequate data were presented to indicate that 100 ppm chloroaniline, or less, in bar soaps would present no hazard to humans even after multiple baths with such soaps.

In addition to the data submissions already referenced, additional references were reviewed to obtain specific background data. Most of these references deal with effectiveness (Refs. 4 through 11), but a few refer to specific problems such as photodermatitis and contact dermatitis (Refs. 8, 9, 10 and 12, 13, 14). The Panel concluded from these references and data submissions that photosensitization and contact dermatitis from triclocarban were of such rarity that they present no major problem to the general user of a soap containing triclocarban.

The question of the percent of active ingredient required to produce a microbial reduction on the skin which can be correlated with significant odor reduction unfortunately cannot be answered with certainty. Independent studies to show effectiveness, as measured by standard handwashing studies, OTC Volumes 020031, 020044 to 020046 (Ref. 1 and 5), have produced a variety of reduction values depending on active ingredient(s), their concentration, number of subjects, initial variation in the hand count of the subjects, and the method of analysis. Marketed soaps containing 1.5 percent triclocarban have been tested for effectiveness as measured by handwashing tests and have produced values ranging from 80 to 90 percent reduction (Ref. 15). The deficiencies inherent in the consideration of reduction in such simplistic terms should be recognized. Data compiled from several studies, unfortunately frequently conducted with an inadequate number of subjects, suggested a reduction of approximately 80 percent with a 1 percent soap. No significant difference was shown with a 1.5 percent soap.

Claims have been made for greater odor reduction with the 1.5 percent soap formulation based on odor evaluation tests. However, such tests are highly subjective and reliable only when rigidly controlled and analyzed with an appropriate statistical model. Tests to evaluate odor should be correlated with tests of microbial reduction in the same study with an adequate number of subjects.

Handwashing studies must be performed with an increased number of subjects (see suggestions for Cade and Quinn Handwashing Studies in the Specific Protocols) selected from individuals with a specified high initial count on the hands. The studies must have appropriate analysis with statistical procedures designed to account for high initial variation, such as analyses of variance and covariance and hypothesis testing including power calculations of the reduction found with use of the test product against an expected or established reduction.

On the basis of risk/benefit considerations the Panel concludes that the only permitted use of triclocarban should be as an antimicrobial ingredient in bar soap at a concentration not to exceed 1.5 percent and only for a period of 1 year following publication of the final monograph in the FEDERAL REGISTER. During this period, testing where applicable, as outlined in the "Guidelines for Safety and Efficacy Testing of OTC Topical Antimicrobials" should be performed. Data to be developed must include absorption and blood level studies in humans; identification of target organ(s) in chronic studies to resolve questions of potential testicular, brain or splenic changes with concomitant blood levels where changes occur; reproduction studies; studies to determine the effect of glucuronide deficiency in infants; and demonstration of substantivity over time in various body areas including the amount of triclocarban deposited on the skin from a single bath.

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TRICLOCARBAN

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CLOFLUCARBAN

2. The OTC Antimicrobial I Panel has reviewed the safety and toxicity data submitted and has concluded that adequate safety and effectiveness data are not yet available to permit final classification of cloflucarban (TFC, CF_3, 3-trifluoromethyl, 4, 4' dichlorocarbanilide) for use in bar soaps. Other applications were not considered.

The Panel concluded that enough data were submitted to convince them that there is no known hazard to the public from the continued use of cloflucarban in bar soaps at the maximum concentration and for the interim period specified below. The basis for this was the oral LD_{50} of cloflucarban in rats as compared with hexachlorophene. The oral LD_{50} for cloflucarban is reported to be in excess of 5 gm/kg body weight while the LD_{50} for hexachlorophene is only 0.12 gm/kg as reported in OTC Volume 020133 (Ref. 1). Also, based on blood level data for cloflucarban (which is not complete at this time), the Panel does not consider cloflucarban as toxic as hexachlorophene. Therefore, the Panel recommends that cloflucarban (or a combination of cloflucarban with triclocarban) when used in bar soaps, not exceed a total concentration of 1.5 percent and that this recommendation be permitted to extend for a period of 1 year following publication of the final monograph in the FEDERAL REGISTER in order to allow interested parties time to conduct the necessary research to correct the deficiencies listed below.

At the beginning of the work of the Panel there was a paucity of information submitted on the safety and effectiveness of cloflucarban. Since that time, additional data have been submitted to the Panel for consideration. However, the Panel still finds several areas of deficiencies in the data base. One of these is the lack of blood level data following topical application. In fact, no data were submitted showing the following:

a. Substantivity of cloflucarban to the skin following one and several baths using a cloflucarban-containing bar soap.

b. Degree of absorption of cloflucarban following deposition on the various types of skin (young, mature, aged, diseased).

c. Peak blood levels following multiple baths.

d. Metabolic rate and fate of cloflucarban in the body.

e. Tissue storage of cloflucarban.

It is the Panel's opinion that final classification of cloflucarban for use in bar soaps cannot be made until such data are provided.

From a purely toxicological viewpoint, the Panel believes that inadequate data were submitted showing a dose/effect relationship. Conflicting data were submitted that were at such variance that inter-laboratory differences could not possibly account for the discrepancies. For example, data in OTC Volume 020133 (Ref. 1) showed that cloflucarban caused testicular effects in rats after 4, 8, 11 and 13 weeks of study at the lowest oral feeding level, 25 mg/kg, and liver changes at 1,000 mg/kg. This study showed that a "no-effect" oral feeding level was somewhere below 25 mg/kg (OTC Volume 020133, Tab 16). In contrast to this study, another study in Volume 020166, Tab 1 (Ref. 1) indicated that the "no-effect" oral level was 100 mg/kg with no testicular or other pathologic finding.

The Panel therefore was presented two controlled studies with widely varying results. It is the recommendation of the Panel that these discrepancies be resolved through adequately controlled research which will show the "effect" and "no-effect" level in the same study. Just as important is a determination of the "effect" and "no-effect" blood level of cloflucarban. As a word of caution, it should be pointed out that the Panel was presented suggestions in OTC Volume 020133 (Ref. 1) that an adequate analytical procedure for cloflucarban in biologic fluids was not available.

In view of these conflicting data and in the absence of definitive data on absorption through human skin, the Panel recommends to the Commissioner that a limit of 1.5 percent cloflucarban, or a combination of cloflucarban and triclocarban) be set until such time as adequate data relating blood levels and toxic effects are made available.

Data submissions, in OTC Volume 020133, Tab 11, 12, 13 (Ref. 1), to the Panel are adequate at this time to assure the Panel that cloflucarban has no significant potential for the induction of carcinogenesis, teratogenesis or mutagenesis. The Panel therefore does not consider these to be problem areas.

The Panel was concerned about the potential for cloflucarban to cause contact sensitization and, to a lesser degree, photosensitization. More to the point, perhaps, was the lack of adequate research addressing this potential. The papers drawing attention to contact sensitization and to photosensitization are those by Epstein et al. (Ref. 2), Solomon and Bluefarb (Ref. 3) and Masuda et al. (Ref. 4). These authors indicated that the potential for contact or photosensitization from cloflucarban was greater than that from triclocarban, but far less than that from certain other antimicrobial agents.

In the absence of adequate data, it can only be assumed that cloflucarban may have the same route and mode of elimination from the body as triclocarban since they are similar molecules.

A major route of elimination of triclocarban from the body is reported to be via conjugation to the glucuronide in the liver. This mechanism may be deficient in young animals and human infants. The Panel felt that inadequate data concerning elimination and toxicity in young animals were submitted. The Panel recommends that adequate research in young animals with blocked formation or unavailable glucuronide systems can be conducted in order to define the toxicity potential for human infants.

Since the liver is considered the major organ for conjugation, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

Therefore, the Panel recommends that unless such studies as described above are conducted within 1 year following the publication of the final monograph in the FEDERAL REGISTER this ingredient should be restricted from use in infants. The label for the preparation containing the ingredient would state: "Not to be used on infants under 6 months of age." The literature sources documenting the impairment of glucuronide capacity in infants is listed separately under the section on triclocarban.

The deficiencies for cloflucarban related to effectiveness are similar to those for triclocarban and have been discussed in other sections under the Comment concerning Efficacy of Antimicrobial Soap and in the statement of the Panel on triclocarban.

In summary, the Panel has concluded that cloflucarban or a combination of cloflucarban with triclocarban can be used in bar soap at a total concentration not to exceed 1.5 percent and only for a period of 1 year following publication of the final monograph in the FEDERAL REGISTER. The deficiencies discussed for triclocarban, and data required to allow placement of that ingredient in Category I, are similar for cloflucarban. If used in combination with triclocarban toxicity studies will be required to demonstrate that there is no increased toxicity with the combination. The toxicity studies outlined in the Guidelines will be required and should include determination of the oral toxicity including target organ determination with blood levels and "effect" and "no effect" dose in the same study.

The studies for cloflucarban alone are enumerated in the statement on the combination of triclocarban and cloflucarban.

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THE COMBINATION OF TRICLOCARBAN AND CLOFLUCARBAN IN BAR SOAP

The Panel is placing the combination of triclocarban and cloflucarban in Category III. These two chemicals are quite similar in their use, mode and spectrum of antimicrobial action, and, in all likelihood, toxicity. However, it is the view of the Panel that additional data are needed on the individual ingredients. No data were submitted on the toxicity of the combination of ingredients, although it is the understanding of the Panel that such studies are currently being conducted. The studies outlined under the discussion of triclocarban and cloflucarban required to characterize the toxicity of the individual chemicals also apply to the combination and should include determination of substantivity, absorption, distribution, blood levels, excretion and effect/no effect dose with the establishment of toxic effects, especially on the target organ determined in the same study.

Since the excretion of both chemicals from the body is thought to be by the glucuronide pathway, the recommendations for studies and labeling on this aspect should apply also to the combination.

Until adequate studies are submitted to make a final determination, the Panel recommends a limitation of the total combination of triclocarban and cloflucarban to 1.5 percent for a period not to exceed 1 year after publication of the final monograph in the FEDERAL REGISTER.

TRICLOSAN

3. After reviewing the extensive safety and effectiveness data, the Panel has concluded that adequate data are not yet available to permit the final classification of triclosan for use in topically applied antimicrobial products. From the data submitted, the Panel concluded that there was no known hazard to the general public from the use of triclosan in concentrations not greater than 1 percent in marketed products. Based on blood level data (discussed below) triclosan appears to the Panel to be safe for use in such formulations. The Panel therefore recommends that triclosan be permitted for use in topically applied antimicrobial products sold to the general public for a period of 1 year following publication of the final monograph in the FEDERAL REGISTER in order to allow interested parties time to conduct the necessary research to supply data in the areas indicated as deficient in the following summary:

It has been shown in animal experiments (OTC Vol. 020037, Ref. 11) that triclosan can be absorbed through intact skin. This has been verified by Maibach (Ref. 1) and also reported in OTC Volume 020154 (Ref. 11) which details human blood levels following the use of a triclosan-containing soap on intact skin.

The primary target organ for toxicity from triclosan is the liver. There is still a question as to whether the damage to the liver is due to the intact molecule, a metabolite, or a combination of the two (triclosan and/or triclosan metabolite).

A subchronic (90 day) oral study in dogs revealed liver damage at blood levels of 67.4 ppm total triclosan (free triclosan plus metabolite) resulting from an oral dose of 25 mg/kg/day. A no-effect oral dose of 12.5 mg/kg/day, in the same study, resulted in a total blood level of 36.1 ppm (OTC Vol. 020167, Ref. 11). Similar studies, using the same oral dosing regimen, in which blood levels were not determined, showed liver toxicity in dogs (OTC Volumes 020154 and 020034, Ref. 11). The dose-related histopathological damage in the dogs was described as periportal to midzonal hepatocytic degeneration which led to focal necrotic hepatitis. This change appears to be reversible when exposure to triclosan is terminated (OTC Vol. 020167, Ref. 11). In other studies, when triclosan was administered in the diet to dogs or rats for 90 days, at doses equivalent to those used in previously discussed studies, no liver damage resulted (OTC Volumes 020166 and 020167, Ref. 11).

Insufficient data was submitted concerning the toxicity from longer term exposure to triclosan by any route of administration.

Taking into consideration animal toxicity and human absorption and blood levels, safety factors were calculated. It was found in subchronic 90-day dog studies that the highest no-effect dose administered was 12.5 mg/kg. The absolute dose given the dog was 75 mg (12.5 mg/kg×6 kg dog). Extrapolated to man by surface area, using the technique of Paget and Barnes (Ref. 12), the no-effect level might be expected to be 232.5 mg in the human. The value was calculated by multiplying the absolute dose in dogs showing no effect by the conversion factor for surface area (75 mg×3.1).

If we assume that a bar soap contains 1 percent triclosan as the active ingredient and that an average bath consumes 7.0 grams of soap, then the total available triclosan would be 70 mg. If we assume that 1 percent of the 70 mg of the available triclosan remains on the skin as a substantive agent, then a total of 0.7 mg of triclosan would be available for absorption. If we assume that 8.9 percent of the 0.7 mg of triclosan is absorbed (Ref. 1), then 0.062 mg would be in the blood. Thus, the following safety factor, using surface area can be calculated:

$$\frac{\text{232.5 mg (expected no-effect dose level in man)}}{\text{0.062 mg (expected exposure dose in man from 1 bath)}} = \text{3,554-fold safety factor}$$

Another way to calculate a safety factor is to assume that an average size human has 5,000 ml of blood, and if we assume that the 0.062 mg of triclosan is instantaneously absorbed from the skin, the concentration of triclosan (free) in the blood would be approximately 12 parts per billion (ppb). If it is assumed that some segment of the population takes two baths per day, and that the total triclosan is absorbed and accumulates, the blood level would be 24 ppb. Data from the OTC submissions suggest that rapid conversion of free triclosan to the glucuronide occurs, and that within a few minutes, most of the absorbed triclosan exists only as the metabolite. (OTC Volume 020154).

If we take the lowest "no-effect" blood level data (36,100 ppb triclosan/triclosan metabolite) in dogs (OTC Volumes 020182–020185 and 020186, Ref. 11) and recognizing that the data was reported from a 90 day study (Ref. 15), the following safety factor could be calculated:

$$\frac{\text{36,100 ppb}}{\text{12 ppb (blood level of triclosan from a single bath)}} = \text{3,000-fold safety factor}$$

or

$$\frac{\text{36,100 ppb}}{\text{24 ppb (blood level of triclosan from 2 baths)}} = \text{1,500-fold safety factor}$$

Based on the highest "effect" blood level (67,400 ppb triclosan/triclosan metabolite), the following calculation could be made.

$$\frac{\text{67,400 ppb}}{\text{12 ppb (single bath)}} = \text{5,600-fold safety factor}$$

or

$$\frac{\text{67,400 ppb}}{\text{24 ppb (2 baths)}} = \text{2,800-fold safety factor}$$

The above calculations are, as mentioned, based on theoretical assumptions. Preliminary data from humans (Ref. 15) revealing a blood level of 44 ppb of triclosan/triclosan metabolite allow the following calculations to be made:

$$\frac{\text{67,400 ppb (blood level at effect dose in dogs)}}{\text{44 ppb}} = \text{1,531-fold safety factor}$$

$$\frac{\text{36,100 ppb (blood level at no effect dose in dogs)}}{\text{44 ppb}} = \text{821-fold safety factor}$$

These calculations would indicate a substantial safety factor, but it should be pointed out that studies to date, relating blood levels to toxic effects, are short-term studies. Humans may be exposed to bar soap daily over their entire life span. Also, several assumptions were made because of unresolved data; namely, the degree of substantivity, and rate and amount of absorption. These assumptions must be tested to provide clarification. This research should include humans in various age groups and with varying skin conditions.

No evidence of potential mutagenesis, carcinogenesis, teratology or reproductive

effects were found in studies with various rodent species (OTC Volumes 020033, 020034, 020035, and 020154, Ref. 11).

Data indicate that the chemical cannot be considered a primary sensitizing or photosensitizing agent in animals (Volume 020104, Ref. 11) or in humans (OTC Volume 020033, Ref. 11), An incident of hyperpigmentation and irritation from the use of triclosan-containing soap has been reported (OTC Volume 020086, Ref. 11). Studies have not eliminated possible cross-reactivity following previous sensitization with hexachlorophene, salicylanilides or carbanilides and further cross-sensitization studies should be performed.

A major route of elimination of triclosan from the body is reported to be via conjugation to the glucuronide in the liver. This mechanism may be deficient in young animals and human infants. The Panel felt that inadequate data concerning elimination and toxicity in young animals were submitted. The Panel recommends that adequate research in young animals with blocks formation or unavailable glucuronide systems be conducted in order to define the toxicity potential for human infants. Since the liver is considered the major organ for conjugation, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

Therefore, the Panel recommends that unless such studies as described above are conducted within 1 year following the publication of the final monograph in the FEDERAL REGISTER this ingredient should be restricted from use in infants. The label for the preparation containing the ingredient would state: "Not to be used on infants under 6 months of age." The literature sources documenting the impairment of glucuronide capacity in infants is listed separately under the section on triclocarban.

Data submissions (OTC Volumes 020033–020040, 020077, 020079, 020142, 020153, 020166, 020170, 020183, 020185, Ref. 11) and a series of reports with regard to the purported antimicrobial activity of triclosan have been studied, examined, and reviewed. These reports suggest that numerous gram positive bacteria are susceptible to its action at levels comparable to other substituted phenols, such as hexachlorophene. However, some gram positive skin residents appeared somewhat less susceptible than others. The lack of susceptibility of the gram positive streptococci is a potential hazard (see discussion of glomerular nephritis in comments for antimicrobial bar soaps). In attempts to define the spectrum of triclosan, some of the gram negative bacterial strains listed in the reports were revealed to be susceptible to triclosan. Those gram negative bacteria showing in vitro susceptibility to triclosan included strains of the various coliforms, *Proteus* and *Salmonella*. One type of gram negative organism of increasing importance in the hospital environment which was found to be quite resistant was *Pseudomonas aeruginosa*. Other microorganisms showing low levels of susceptibility included various fungi and viruses, such as the polio virus. Influenza, adeno- and vaccinia viruses are inhibited at a lower concentration. The reports suggest that reduction of the number of microorganisms in the skin microflora with the use of triclosan in soaps is similar to that with other bisphenols.

Some reports suggest the *Pseudomonas* can be selectively established at high levels on the skin with the topical use of bisphenols (Ref. 2, 3 and 4). In addition, triclosan can be utilized for the selective isolation of *Pseudomonas* from materials containing both gram positive and gram negative organisms. These materials include foods and microflora samples from the skin (Ref. 3 and 5). This isolation is facilitated with the use of a patented *Pseudomonas* isolation agar containing triclosan (Ref. 13).

Triclosan differs form other bacteriostats active primarily against gram positive bacteria, in that it does have in vitro and probable in vivo (Ref. 6) activity against some gram negative bacteria, but unfortunately not against *Pseudomonas*. With the widespread use of antibiotics and disinfectants selectively active, primarily against gram positive bacteria in the hospital environment, gram negative, nosocomial infections are increasingly life-threatening (Ref. 7) especially *Pseudomonas*. With the environmental pressures being pushed in one direction (one-way selective pressure) toward the selection of gram negative organisms, i.e., *Pseudomonas*, in the hospital environment, unexpected reservoirs and mechanisms of transmission are being reported (Ref. 8 and 9). It is essential to eliminate sources of gram negatives in particular areas of the hospital, for instance, burn units, intensive care units in which immunosuppressive drugs are administered and in neonatal nurseries. One study by Bodey and Rosenbaum (Ref. 10) describes the use of a triclosan-containing soap in hospitalized and immunosuppressed patients. This study reports the results of the bathing of leukemic patients in a protected environment (Life Island) with a bar soap containing 1 percent tribromsalan and 1 percent triclosan. The authors report reduction in total counts on various body sites, especially staphylococcal species. It is the Panel's view that the results of this in vivo study cannot be projected as applicable in a normal environment. The environmental problem with triclosan proposed by the Panel is foreseen as a problem in personnel transmission with *Pseudomonas* carriage on the hands as a result of selective pressures and with the widespread continuous use of triclosan-containing products in the hospital environment. Furthermore, the patients in this study, which had no controls, were all immunosuppressed and receiving concomitant antibiotic therapy, both oral and topical.

In addition the skin sampling and culture techniques were not optimal for the isolation of *Pseudomonas* from the skin. The serious possibility of carryover of inhibitory antibiotic residue from the topical therapy would invalidate the cultural results. This is a well-conceived study with application for these particular patients. However, there is certainly a risk involved with the knowledge that the soap being applied has no activity against *Pseudomonas* and undemonstrated claimed in vivo activity against other potential pathogens. In a subsequent publication (Ref. 9), these same authors describe another sutdy of this type and conclude that although 76 percent of aerobic bacteria were eliminated by cleansing with a soap containing a combination of triclosan, and tribromsalan, strains of potential pathogens such as *Enterobacter* species, a *Klebsiella* species, *Proteus* species and *P. aeruginosa* persisted. Thirty-three percent of the patients had persistent pathogenic bacteria and 40 percent had persistent fungi. Despite intensive systemic and topical antibiotic therapy and washing with an antimicrobial soap as a protective measure, the organisms persisting are those most likely to cause fatal infections in these seriously ill patients.

In the judgment of the Panel, clinical effectiveness in the prophylaxis and treatment of superficial pyogenic infections of the skin has not been established. Deodorant effectiveness has been demonstrated in the reports reviewed, but safer, alternative agents for the reduction of body odor exist.

The Panel has reviewed the use of isolation medium containing triclosan for the selective isolation of *Pseudomonas* from the skin. This fact per se would not indicate a problem with the environment nor is this the basis of the Panel's conclusions about triclosan in the hospital environment. Current thought among scientists investigating skin microflora raises the possibility that this chemical applied to the skin, considering the skin as a possible culture medium superior in many instances to those devised by microbiologists, would also act selectively to promote the shift of the skin flora especially in environments where *Pseudomonas* is ubiquitous and life-threatening to many patients.

The further widespread use of a product containing an antimicrobial agent with some gram negative activity, but with little activity against *Pseudomonas*, might easily shift the microbial flora of the skin, especially on the hands after repeated daily use, to allow carriage of high numbers of potential pathogens on the hands of hopsital personnel (Ref. 9 and 14).

Because of this potential for influencing the gram negative population and/or the addition of another potential selective agent for *Pseudomonas*, the Panel recommends that triclosan-containing products not be used in the hospital or other closed environments such as nursing homes, where individuals are present who may be highly susceptible to infection with microorganisms from the environment not normally pathogenic (opportunistic pathogens).

This restriction on the use of triclosan also applies to any combination products containing triclosan. Triclosan should be used only in products where there is no exposure to persons with debilitating dis-

eases, physical debilitation, persons who are immunologically compromised or where the closed environment in the hospital or other institution would possibly allow the shift of environmental pressures toward *Pseudomonas*.

Many animal toxicity studies for this ingredient have been submitted and discussed above. Further work is necessary to determine whether the triclosan molecule, the metabolite or a combination produce the toxic effect. More data on human blood levels following topical application are needed. A variety of skin areas, types and conditions should be studied. Possible mounting of blood levels with the use of multiple products should also be investigated.

It was the view of the Panel that in vitro data indicate activity against some gram negative microorganisms but that further verification of the spectrum is required as well as in vivo demonstration of activity against *Proteus, Salmonella,* and *Pseudomonas aeruginosa*.

Studies relating the use of triclosan in the hospital or closed environment to the incidence of gram negative, and particularly *Pseudomonas,* infections may be difficult to perform since the infection rate depends on many factors. Necessarily, some approach to a solution must be made since the theoretical reasoning of an effect follows general ecological principles. Further in vitro and in vivo susceptibility work will establish the actual spectrum of this chemical on the skin since the Panel was presented with conflicting reports.

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(14) Brown, D., Abstract of paper presented at the American Public Health Association Meeting, San Francisco, 1973 is included in OTC Volume 020186.

(15) Testimony presented by DeSalva, S. J., before the Antimicrobial I Panel during the open session of November 29, 1973 s included in OTC Volume 020186.

IODOPHORS

4. The OTC Antimicrobial I Panel recognizes the existence of at least three categories of iodophors: (1) Solubilized inorganic elemental iodine, such as tincture of iodine, USP, or the aqueous iodine-iodide solubilized product; (2) iodine complexed or combined with various surfactant compounds such as poloxamer-iodine complex; and (3) iodine complexed with various non-surfactant compounds such as PVP-iodine complex (polyvinyl pyrrolidone-iodine). The antimicrobial activity of all of these agents is dependent upon the release of elemental iodine. Iodine is recognized to be a broad spectrum antimicrobial with activity against fungi, viruses, and both gram positive and gram negative bacteria.

a. *Solubilized inorganic elemental iodine.* Iodine has a long history of use as a broad spectrum antimicrobial agent. There is an extensive literature documenting the effectiveness of aqueous and alcoholic solutions of elemental iodine as an antimicrobial. In fact, the United States Pharmacopeia has listed iodine preparations since 1840. In the judgment of the panel, elemental iodine hydroalcoholic solution is safe and effective when properly used on unbroken skin as a patient pre-operative skin preparation but its irritating properties and delay in wound healing make it unsafe for other uses. (See discussions in Categories I and II of tincture of iodine.) The data supporting these positions may be found in reference books such as those by Lawrence and Block (Ref. 1) or Hugo (Ref. 2) and Sykes (Ref. 3) as well as the numerous articles contained in OTC Volume 020181 which is an extensive bibliography of references about iodine (Ref. 4).

A variety of values has been proposed for the minimum concentration at which iodine is lethal to cells. It has been stated by Sykes (Ref. 3) that all microorganisms are killed by the same concentration. However, the organic load (in a wound, with serum, or on the skin) and pH (acidity) may dramatically change the concentration required to achieve the desired killing effect on the skin. It is difficult to set a level of free iodine which is effective against all types of microbial flora: Viruses, fungi, spores, and vegetative bacteria. The variables present in any situation where iodines are used as bactericidal agents on the skin must be tested in in vivo human studies because it is necessary that they be controlled in experiments testing effectiveness against high microbial populations. The results of these studies should be used to determine use dilution and label directions. It is probable that no single value in ppm of iodine can be established as universally effective. Elemental iodine is discussed in this statement since the effectiveness of all iodophors is dependent on the release of free iodine as the active agent and the complexing molecule acts only as a carrier.

b. *Iodine complexed with various surfactant compounds.* The Panel recognizes that elemental iodine complexed with a surfactant type "carrier" molecule reduces the amount of immediate "free" iodine, since most of the formulated iodine is bound in the complex. The Panel was not presented adequate data to determine if the complex is really a micellular solubilization of iodine at the molecular level or whether loose chemical bonding exists producing what could be termed a "sociable moiety". Indeed, the complexation of iodine with the carrier molecule is responsible for the changes in characteristics observed in staining, burning or irritation of the skin. The amount of "free" elemental iodine in solution is a function of the equilibrium constant of each complexing formulation. If all of the "free" elemental iodine is removed from solution (as in the case of application to a wound where potentially all iodine present is bound by total organic load), then a finite period of time would be required before a new equilibrium would be established. Once the iodine is released from the complex, it acts as elemental iodine, a broad spectrum antimicrobial agent. After release of iodine, the carrier molecule remains at the site as any other similar surfactant molecule.

The Panel has concluded from the data submissions that iodine complexed with a surfactant is a way of presenting iodine as an antimicrobial agent to a wound site or the skin. The purpose of presenting iodine in such a form is to reduce the staining and toxic (locally) properties inherent in the iodine molecule. Since most of the formulated iodine is tied up in the complex, the amount of "free" iodine available at any given instant is relatively small. Therefore, theoretically, the degree of irritation should be lessened. Indeed, the data submitted does substantiate a reduced degree of iodine burn from the complex. In many cases, the area covered by the iodophor may be covered with adhesive tape or bandaged because the amount of "free" elemental iodine is not enough to cause tissue burns. This is a significant advantage for these iodine preparations over older iodine formulations, such as tincture of iodine. The concern of the Panel has been that this advantage of complexed iodine may also be its most serious disadvantage. The advantage of the iodophor is that the area can be treated and bandaged without irritation, while the serious disadvantage may be that actually there is less free iodine as an active antimicrobial. The Panel was presented no significant data about the "release" or disassociation of iodine from the com-

plex. Additionally, the Panel was concerned about the lack of stability data on iodophor formulations.

The Panel is aware of the proposed mechanism which has been described in U.S. Pat. 3,028,299 (Ref. 11) and by Schmidt and Winicov (Ref. 5) theorizing the establishment of an equilibrium between free iodine and complexed iodine. The labeling for a given product states the amount of available or titratable iodine in the formulation. However, only a fraction is in the "free" elemental iodine form at the time of use. The concern of the Panel was the lack of data in the cases of actual use of the product which identifies the fraction that is "free". For example, once the "free" elemental iodine is bound to an organic load (in a wound, with serum, or on the skin), how rapidly is new elemental plex take place at the same rate in the plex? Does pH influence rate of release? (See OTC Volume 020077, Tab 118, Ref. 4). Only preliminary data were presented in the form of rapidity of titration with thiosulfate or rapidity of partitioning between two immiscible solvents. The Panel considers this form of data inadequate since it does not reflect actual conditions of use. For example, will the dissociation of iodine from the complex take place at the same time in the presence of iodine bound to an organic load? No such data were submitted to the Panel and before final classification of these iodophors for most applications can be made, such data are necessary.

Another area of concern for the Panel was the lack of stability data submitted for the several iodophor preparations. It is recognized that elemental iodine is a rather powerful oxidizing agent, as are all the halogens. It was suggested that some iodophors are not stable over a two year shelf life period (Ref. 12). The Panel recommends that the Food and Drug Administration ascertain the stability of iodophor products.

The Panel has concluded that inadequate safety data were presented for all applications to permit final classification of these surfactant iodophors at this time. Some data submitted to the Panel in OTC Volume 020119 (Ref. 4) suggest that with certain of the surfactant idophors the volatile characteristics of iodine are not changed. In an occluded environment such formulations may corrode the tissue resulting in tissue burns. It was also suggested in this same volume, that all surface active agents cause hemolysis and tissue irritation and for this reason all surfactant-containing iodophors should be removed from soft tissue or surgical wounds prior to their closure. The Panel noted only a very small number of clinical studies with the surfactant iodophors which could shed light on these problems. The Panel recommends that surfactant iodophors be studied to define retardation of wound healing and irritation before they are labeled as Skin Wound Cleansers. For all other uses the following controlled studies using both research laboratories and clinics should be conducted: Blood levels of iodine (and iodide) and/or the carrier or complexing molecule following various types of usage of the product; systemic toxicity after absorption of the carrier molecule (animals only); the target organ for toxicity from the carrier molecule as well as metabolic fate of the carrier molecule (animals only).

One of the primary concerns of the Panel was the influence of surfactant iodophors on rate of wound healing. Conflicting data were presented to the Panel in the area of effect on wound healing. For example, several citations were submitted indicating little or no effect from the iodophor on rate of wound healing (See OTC Volume 020071, Tab 49, Tab 90). In contrast to these, data were presented suggesting that certain nonsurfactant iodophors (PVP–iodine type) delay the rate of wound healing see Custer et al. (Ref. 6) and Edlich et al. (Ref. 7). In attempting to resolve this question, the Panel noted a paucity of controlled research that would define whether any delay in wound healing is due to iodine, carrier molecule or the combination. It is therefore, recommended that definitive research be conducted on each surfactant iodophor used in or on wounds and the results of such research be reported to the Food and Drug Administration for final evaluation.

Another primary area of concern of the Panel was the paucity of clinical evaluation data dealing with the claimed effectiveness of most of the surfactant iodophors. There were many in vitro tests reported and the Panel is satisfied that, under the specific conditions of test for the in vitro evaluation, the specified iodophor had the stated antimicrobial effects. The Panel does feel, however, that clinical claims made from extension of the in vitro data were largely unwarranted in the absence of clinical research. The Panel again recommends that controlled clinical studies be conducted on each surfactant iodophor for which a specific claim is made.

In specifying some shortcomings in the data submitted, the Panel does not infer that a known hazard exists with these products. On the contrary, the Panel did receive enough toxicity data to convince them that there is no known hazard to the public from the use of these iodophors.

c. *Iodine complexed with non-surfactant compounds.* The only example of this non-surfactant type iodophor was polyvinyl pyrrolidone-iodine complex (PVP-iodine). Some testimony was presented to the Panel suggesting that PVP-iodine is a distinct chemical entity, while other testimony suggested that PVP-iodine is only a complex of polyvinyl pyrrolidone and iodine. In the absence of definitive data, the Panel is referring to PVP-iodine as a complex. Some evidence was presented that indicates iodine is released more slowly from PVP-iodine complex than from the surfactant-iodine complex. The Panel would require the same rate-of-release data in the presence of an organic load for the PVP-iodine complex.

The Panel has concluded that all defined uses for PVP-iodine will be placed into Category III for a period of 1 year following publication of the final monograph in the FEDERAL REGISTER in order to allow adequate time to obtain the data specified below. Enough data were presented to the Panel to satisfy them that no known hazard to the public would result from the use of PVP-iodine. The specific areas of concern that caused the placement of this iodophor into Category III follow.

Data were presented to the Panel that indicate that PVP-iodine preparations were used in volume on large burn areas, on vaginal mucosa, in large open wounds and in abdominal surgery. Following such indiscriminate use, it was shown that some individuals showed altered protein bound iodine (PBI) levels and thyroid function. Therefore, the Panel recommends that more controlled research be conducted to show the conditions of use under which thyroid function would or would not be altered, and the amount of PVP-iodine required to induce alteration. The Panel would be more interested in data with current analytical procedures, such as T3 and T4 levels, than in PBI levels (Ref. 4).

The Panel was presented conflicting data concerning the role of PVP-iodine use on the rate of wound healing. Some data suggested that PVP-iodine had no effect on rate of wound healing while other data suggested a delay in wound healing after the iodophor use in animal model studies by Custer et al. (Ref. 6) and Edlich et al. (Ref. 7). In the opinion of the Panel, inadequately controlled studies were reported and are of only limited value in making a final judgment as to effect on wound healing. The Panel recommends controlled studies be conducted to answer the question as to the cause for delay in wound healing, if it occurs. The iodine, PVP alone, formulation aids, and final product should be evaluated in a controlled study.

While reviewing the data submission, the Panel was concerned about stated label claims made without adequate supporting clinical data. Statements implying "long-acting germicidal" activity or prolonged viricidal or sporicidal activity with iodine suggested clinical effectiveness over relatively long periods of time. Two questions arose from such implication: (1) What is the rate of release of "free" iodine from the complex in a clinical application and (2) what is the evidence of "germicidal" activity over a period of time in a clinical application? The Panel recommends that definitive research be conducted to answer these questions as well as to define the parameters or limiting conditions for the germicidal activity of iodine, whether free or bound in an iodophor.

Reports have appeared in the literature which have indicated possible lymph node changes by circulating polyvinyl pyrrolidone. See Ashwood-Smith (Ref. 8), Towers (Ref. 9) and Dupont and Lachapelle (Ref. 10). The Panel recognizes that certain molecular weights of polyvinyl pyrrolidone have been used as plasma expanders which have caused the node changes. PVP-iodine prepara-

tions have been used in large open wounds and in the abdominal cavity, but the Panel feels that inadequate data were made available to prove positively that such lymph node changes do not take place following such uses of PVP-iodine. The primary recommendation for additional work in this area is to show the extent of scavenging of residual PVP-molecules by the reticuloendothelial system and possible lymph node involvement following use in abdominal cavities or in large wounds. The Panel was convinced by testimony which is summarized in OTC Volume 020149 (Ref. 4) from Dr. G. Rice of the National Cancer Institute and submitted data that there was little, if any, danger of carcinogenesis from residual PVP molecules.

The general deficiencies noted with the iodophors involve both safety and effectiveness. The whole question of iodine release from the complexed molecule including rate of release and binding to other materials, as well as the influence of the release rate on effectiveness must be resolved. The stability of complexed iodine over time and with varying environmental conditions must be known and and controlled so a stable product is marketed and effectiveness can be assured. The systemic absorption of topically applied iodine must be measured using the currently accepted assay procedures. In many cases, the toxicity of the carrier molecule has been only superficially characterized. Further detailed studies are necessary before toxicity can be determined (see discussion of animal toxicity in guidelines).

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QUATERNARY AMMONIUM COMPOUNDS

5. Since the first introduction in 1935 of quaternary ammonium salts ("quats") with surface active characteristics used as antimicrobial agents, there has been wide use and acceptance of these compounds as antiseptics and disinfectants. There has also been much controversy concerning the microbial spectrum, inactivation with incompatible materials, and potential hazard as a result of gram negative contamination, particularly with *Pseudomonas.*

Quaternary ammonium compounds are cationic surface active agents. They can be differentiated from nonionic and anionic surface active agents in that they are basically organically substituted ammonium compounds which can be characterized by the following general representation: $[R_1R_2NR_3R_4]^{(+)}X^{(-)}$. "R" represents a lipophilic group such as long chain hydrogen alkyl or aryl-alkyl radicals or other groups; "X" represents a negative ion such as a halide, sulfate or other radical and "N" represents nitrogen.

The inherent nature of this type of molecular structure allows the synthesis of a large number of variants. The challenge has been met by the production of extremely large numbers of these compounds. The Panel has reviewed only three of these, restricting their comments to those for which data were submitted: Benzalkonium chloride, benzethonium chloride, and methyl-benzethonium chloride. It should be understood, however, that these compounds do contain characteristics which are common to the whole class of quaternary ammonium compounds. The microbial spectrum does not vary significantly from compound to compound.

There is an interference action between cationic and anionic surface active agents with the result that these ionic types of compounds cannot be formulated together without inactivation of the germicidal activity of both compounds. Further discussion of the subject can be found in texts by Lawrence and Block (Ref. 1) and Sykes (Ref. 2). In contrast, the nonionic compounds are often formulated with cationic "quats" in products known as germicidal detergents.

"Quats" and all surface antibacterials have been shown to affect membrane permeability. Indeed, this group of compounds have been called membrane-active. Many authors have recorded the loss or leakage of cell contents after exposure to "quats." Specific transport mechanisms may also be affected. "Quats" probably produce a generalized breakdown in the semipermeable characteristics of the membrane as discussed by Hugo (Ref. 3), Lawrence and Block (Ref. 1) and Sykes (Ref. 2).

Gram positive microorganisms are generally more susceptible to the effect of the "quats" than gram negatives.

The "quats" are non-specifically adsorbed to the cell membrane. In any case, the unprotected cell membrane is sensitive to the action of the "quats". Difference in sensitivity is conferred by access to the cell membrane.

This difference is probably due to the differences in the cell wall of gram positive and gram negative microorganisms. The adsorptive character of the cell wall probably determines the ability of the quaternary to reach and affect the cell membrane beneath the cell wall.

Early reports of the bactericidal activity of "quats" in low concentrations could not be supported when adequate neutralizing chemicals were added to the culture medium for testing antibacterial activity. In early tests, enough "quat" molecules adsorbed to the cells were carried over into the subculture medium to prevent the cells from growing when transferred to culture media. The meaning of the results of such tests was misjudged and misinterpreted during the early effectiveness testing of the "quats".

The gram negative *Pseudomonas* species are frequently resistant to destruction by "quats." The lack of lethal activity of "quats" against *Mycobacterium tuberculosis* has been well established and is reported by Sykes (Ref. 2). The fungicidal activity of "quats" is questionable and "quats" also lack significant antiviral activity. Tables listing the spectrum of "quats" against a variety of microorganisms are numerous and examples can be found in Lawrence and Block (Ref. 1) and Sykes (Ref. 2).

The presence of organic materials substantially reduces the antimicrobial effectiveness of "quats". Their surface active nature permits easy adsorption on surfaces of even glass and plastic and consequently, residues of "quats" may remain. In fact, the adsorption of "quats" onto the bacterial cell surface and subsequent carry-over to the sub-culture medium in testing accounts for early exaggerated claims of effectiveness for "quats."

The cationic "quats" are inactivated by anionic compounds, soaps, Tween 80, and sodium lauryl sulfate as well as by certain metallic ions. Hard water and acidity also reduce the activity of the "quats". These incompatabilities are discussed by Lawrence and Block (Ref. 1) and Sykes (Ref. 2).

Because of their reported low toxicity and ease of use, especially with detergents, these compounds have been widely used for dipping solutions and "cold" instrument sterilization in hospitals. Organic material is commonly added to the solutions and as a result of failure to clean materials or replace old solutions, added micro-organisms are not inactivated and can grow and reproduce. Several serious outbreaks of gram negative infection, as well as infections caused by other organisms, have been reported as a result of contaminated quaternary ammonium solutions (Ref. 7, 9, 10 and 14 through 21).

Preservative ingredients can be added to quaternary ammonium salts to prevent the growth of gram negative microorganisms, particularly *Pseudomonas*. Such a preservative system must be adequately challenged by effectiveness testing. The minimum acceptable standard for challenge testing of the preservative system would be the USP XVIII Preservative Test (pages 845–846) and chemically, the Antimicrobial Agents-Content Test (pages 902–204).

It is the finding of the OTC Antimicrobial I Panel that adequate safety and effectiveness data concerning these specific cationic surface active agents (benzalkonium chloride, benzethonium chloride, methyl benzethonium chloride) are not available to permit final classification except as a Skin Wound Cleanser.

Human systemic absorption and toxicity after topical application cannot be established based on a review of the scientific literature or submitted data. The systemic toxicity of "quats" in animals is low. The LD_{50} and chronic oaral study values in OTC Volume 020179 (Ref. 4) in several animal species are reported. The toxicity reported is indicative of and reflects the surfactant nature of the molecule. The "use dilution" for the "quats" is usually about 1/750 for topical application.

Specific absorption and systemic levels in humans have not been reported for the three "quats" reviewed. Considering the concentrations applied, and extrapolating from animal studies, toxic effects at use levels would be unlikely.

The irritating nature of quaternary compounds on the skin, mucous membranes and in the eye have been reported extensively in the submissions and are found in OTC Volumes 020017, 020018, 020128 and 020143 (Ref. 4). The degree of irritation is dependent on concentration and/or occlusion. There is little irritation potential with the use concentrations.

Various reports of toxicity related to the detergent nature of these compounds have been published. Landsdown and Grasso (Ref. 5) reported that repeated application of 1 percent benzethonium chloride to the skin caused damage with cellular degeneration. "Quats" have been shown by Bettley (Ref. 6) to alter the permeability of the human skin to sodium and potassium ions and to cause enhanced percutaneous absorption. Also, occasional reports of non-allergic and allergic contact dermatitis have been made by Plotkin and Austrian (Ref. 7), Malizia et al., (Ref. 8), Lee and Fialkow (Ref. 9) and Saunders (Ref. 30).

Necrotic ulceration has occurred where detergent creams containing "quats" have been applied to moist areas of the skin of the genitals and buttocks under occlusion as reported by Coles and Wilkinson (Ref. 10) and Tilsley (Ref. 22).

A number of published articles deal with the toxicity of the specific "quats" reviewed by the Panel (Ref. 23, 24, 25). References to sensitivity and contact dermatitis produced with "quats" have been reported (Ref. 26 through 29).

One aspect of the result of the use of "quats" deals with both effectiveness and safety. Over the years since their introduction, the variety and frequency of their use has increased. Several reports by Plotkin and Austrian (Ref. 7), Malizia et al., (Ref. 8), Lee and Fialkow (Ref. 9) indicate systemic infections by *Pseudomonas aeruginosa* and other gram negative bacteria resulting from contamination of detergent fluids in which surgical instruments had been stored. Refer also to other pertinent work concerning nosocomial infections (Ref. 7, 9, 10, and 14 through 21).

The Panel concludes that the effectiveness of the "quats" appears to be limited and their effects in vivo on either resident cutaneous flora or on potentially pathogenic transients on the skin have not been clearly demonstrated. This conclusion is based on the relevant factors which follow.

While the growth of *Staphylococcus aureus* and certain other gram positive bacteria is inhibited by low concentrations of the "quats" in vitro, their reaction to these substances within the cutaneous ecosystem has not received sufficient attention. Since it has been shown by Ogden et al. (Ref. 11) and Sykes (Ref. 2) that "quats" are rapidly adsorbed to proteins and to cotton fibres and their germicidal activity is reduced in the presence of serum and of soap, their efficacy on the skin or in superficial wounds is much less than would appear from results obtained with in vitro procedures.

Many gram negative bacteria are resistant to the germicidal action of "quats", and some strains of *Pseudomonas* can survive and multiply in aqueous solutions to these substances. Such strains may be resistant to related preparations as has been described by Adair et al. (Ref. 12). Strains of the same species can also vary in their sensitivity to the "quats" and this attribute can change as a result of artificial culture as shown by Carson et al. (Ref. 13). In vitro testing of a series of strains recently isolated from human infections and other appropriate habitats must be understaken before the germicidal effects of the "quats" on gram negative species can be satisfactorily assessed.

Mycobacterium tuberculosis, some species of *Clostridia*, most dermatophytes and many viruses are not inactivated by the "quats". There are few reports on the in vitro or in vivo susceptibility of pathogenic fungi or protozoa to "quats".

Various reports show that the application of "quats" to the skin reduces both the bacterial count on hands and in the axilla with subsequent reduction of body odor. There do not appear to have been any studies on the composition of the residual bacterial populations. A reduction of the density of normal skin microorganisms may be followed by a selective increase in the populations of potentially pathogenic microorganisms. Studies of the qualitative effects of "quats" on the skin should be undertaken to insure that inhibition of the normal microbial flora does not produce results which are hazardous to the human host.

The three quaternary compounds reviewed by the Panel have been widely used for many years. Further toxicity data characterized by the absorption and systemic toxicity in a rodent and nonrodent species should be generated prior to the placement of these "quats" into Category I for uses other than as a skin wound cleanser. Also, the in vivo effectiveness of these ingredients for the product categories other than Skin Wound Cleanser needs to be evaluated with modern techniques, including the use of specific neutralizers.

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PHENOL 1.5 PERCENT OR LESS IN AQUEOUS/ALCOHOLIC SOLUTION

6. Lister first demonstrated the usefulness of carbolic acid (phenol) as a germicide in the surgical theater in 1867. Although it has been used since then, the topical use in particular has declined in recent years with the availability of new antimicrobials. Its germicidal mode of action is as a protein denaturant. An easily dissociated complex of the plenol molecule and protein is formed. This complex formation permits the penetration of phenol through intact or abraded skin, mucous membranes or subcutaneous tissues with which it comes in contact. Phenol also may gain access to the pulmonary circulation through inhalation of its vapors (Ref. 1). Many of the toxic effects discussed occur when phenol is absorbed at levels of 1.5 percent or less. However, toxic effects are more serious at concentrations greater than 1.5 percent. (See discussion of phenol greater than 1.5 percent.)

Although phenol is no longer a significantly used antimicrobial, it is still formulated in topical products and there is a large body of literature concerning its effectiveness (Ref. 2, 3, and 4). Phenol was widely used and accepted as an antiseptic when little else was available and its use is certainly historically important. However, it is now obvious that the level of phenol required in a formulation to be effective is frequently so high that it cannot be used safely on the skin (Ref. 5).

Phenol can be bacteristatic or bactericidal depending on the concentration. Phenol is not sporicidal.

The mechanism of action on the microbial cell is very likely the disruption of the cell wall and precipitation of the cellular proteins (Ref. 3 and 4).

Because phenols have a high oil/water partition coefficient (tendency for phenol to remain in the oil phase), the antimicrobial activity may be decreased in the presence of excess oil or fats. Since many phenol products are formulated as ointments or creams, in vivo studies must be conducted to show the antimicrobial effectiveness of phenol in these formulations. In addition, many of the reported effectiveness tests for phenol published in the literature and/or submitted to the OTC Panel were carried out before the development and use of neutralizers in antiseptic testing.

Phenol is a classic example of a chemical which is metabolized and eliminated from the body by glucuronide conjugation in the liver. This mechanism may be deficient in young animals and human infants. The Panel felt that inadequate data concerning elimination and toxicity in young animals were submitted. The Panel recommends that adequate research in young animals with blocked formation or unavailable glucuronide systems be conducted in order to define the toxicity potential for human infants. Since the liver is considered the major organ for conjugation, the effect of inadequate or impaired liver function on elimination and toxicity should also be determined.

Therefore, the Panel recommends that unless such studies as described above are conducted within 1 year following publication of the final monograph in the FEDERAL REGISTER this ingredient should be restricted from use in infants. The label for the preparation containing the ingredient would need to state: "Not to be used on infants under 6 months of age." The literature sources documenting the impairment of glucuronide capacity in infants are listed separately under the section on triclocarbon.

There is a report that phenol is a cocarcinogen in animal tissue (Ref. 6). The Panel is of the opinion that carcinogenic studies should be done to determine whether in fact, phenol itself may have carcinogenic potential. No information on the teratogenic or mutagenic potential of phenol has been submitted and this data should be developed.

Because of the reports of local and systemic toxicity (Ref. 7) after the use of phenol-containing products covered with bandages over large areas of the body, it is recommended that the use of phenol be restricted to small areas of the skin and that occlusive dressings, bandages or diapers in any form should not be used. Phenol-containing preparations should not be used for the treatment of diaper rash. The label should state, "Warning: Do not use for diaper rash or over large areas of the body or cover the treated area with a bandage or dressings."

It is recommended that the total concentration of phenol in powders and in aqueous, alcoholic or oil formulations be restricted to less than 1.5 percent. When camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent. Chemicals with phenol activity, such as sodium phenolate and secondary-amyltricresols should be considered as phenol in the calculation of the total phenol in any formulation. The amount of phenol available as a germicide will, of course, depend upon the particular formulation and the amount of phenol in a free state. The Panel has determined that phenol may be used in formulations, but at a minimal concentration, for its aromatic characteristics.

It seems apparent that even with its long and illustrious history, the time has come to recognize that the levels at which phenol in aqueous and alcoholic formulations is effective topically are also the levels at which topical and systemic toxicity may occur. The fact that these two elements converge has made it necessary for the Panel to limit the concentration which may be marketed while testing for safety is concomitantly performed. The Panel has described rather severe toxicity with the dosing or application of phenol in animals or man and has limited the concentrations greater than 1.5 percent to Category II. (See discussion of phenol greater than 1.5 percent aqueous/alcoholic.)

Even though the effects of phenol toxicity at lower concentrations are similar, the severity is dependent on the concentration. It is the Panel's view that the demonstration of effectiveness at 1.5 percent or less may be exceedingly difficult but that the use of this concentration does not present a known hazard to the consumer. The toxicity of phenol has been extensively described. The major lack of data is in in vivo efficacy studies with concentration at 1.5 percent or less. In vivo studies performed with modern testing and skin sampling procedures, including the use of neutralizers, are required.

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(3) Hugo, W. B., *"Inhibition and Destruction of the Microbial Cell,"* Academic Press, New York, 1971.

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PARA-CHLORO-META-XYLENOL

7. Very little information was submitted to the Panel with regard to para-chloro-meta-xylenol (Ref. 1). Only a a few acute oral and inhalation studies were submitted. These studies do not indicate a high degree of acute toxicity with an oral LD_{50} of greater than 3 gm/kg in rats.

However, because the information that could be obtained from subchronic dosing by various routes of application, determination of target organ, dermal and mucosal absorption, and metabolic studies are not available, an evaluation of the safety of this chemical in a topical preparation could not be made. In addition, information is not available regarding the effects of para-chloro-meta-xylenol on wound healing. The carcinogenic, mutagenic and teratogenic potential of the chemical which might be used topically for prolonged periods of time has, to the best of the Panel's knowledge, not been evaluated. There were two reports of contact dermatitis associated with para-chloro-meta-xylenol (Ref. 3 and 4).

It has been reported by Zondek and Shapiro (Ref. 2) that para-chloro-meta-xylenol is metabolized by glucuronide and sulfate conjugation. Due to the reported deficiency of metabolic conjugating mechanisms in infants, it is the opinion of the Panel that toxicological safety evaluation of para-chloro-meta-xylenol should include the studies to demonstrate safety in animals deficient in these detoxification mechanisms. Since the liver is considered a major organ for conjugation, the effect of impaired liver function on elimination and toxicity would be important.

Therefore, the Panel recommends that unless such studies as described above are conducted within 1 year following publication of the final monograph in the FEDERAL REGISTER, this ingredient should be restricted from use in infants. The label for a preparation containing the ingredient would need to state: "Not to be used on infants under six months of age". The literature sources documenting the impairment of glucuronide capacity in infants are listed separately under the Statement of the Panel on triclocarban.

A manufacturer of para-chloro-meta-xylenol has indicated to the Panel (Vol. 020067, p. 31, Ref. 1) that further toxicological studies were planned; however, no additional information has been made available to the Panel.

Para-chloro-meta-xylenol is a halogen substituted phenol compound. Many of the comments made for the effectiveness testing of phenol apply here. Halogen substitution increases the antimicrobial activity of phenol derivatives. The halogen in the para-position to the hydroxyl group is considered the most effective substitution. Thus, the indications are that this compound would show good in vitro activity. Very little information about the in vivo activity on the skin is published or was submitted to the Panel. At least one report, by Colebrook and Maxted in 1934 (Ref. 5), using a serial washing technique indicated only a slight effect on resident bacterial flora of the skin. Another study reported approximately a 70 percent reduction in microbial count of the flora of the hands after 10 days of use.

Para-chloro-meta-xylenol is primarily active against gram positive organisms with activity against gram negative microrganisms in vitro. Fungicidal activity in vitro is also reported (Ref. 2). The phenol coefficient is reported to be around 40, but the results vary (Ref. 2).

Claims for broad spectrum activity have been made for this compound. It has been tested as a preservative for cosmetic products (Ref. 2). Unfortunately the data submitted are not adequate to support these claims.

Very little effectiveness data which could be evaluated were submitted. Many studies were old and not performed with modern antiseptic testing procedures.

Effectiveness testing both in vitro and in vivo should be done in accordance with the Guidelines developed by the Panel. There are so little data available that it is the view of the Panel, that this ingredient should be tested as if it were a new chemical entity for use in antimicrobial formulation(s).

Only the most superficial toxicity data in animals have been reported to the Panel. It is the Panel's view that toxicity in rodent and non-rodent species, substantivity, blood levels, distribution and metabolism as well as any subsequent systemic absorption studies must be characterized before this ingredient can be considered for placement in Category I. The carcinogenic, mutagenic and teratogenic potential of this ingredient must be determined before it can be listed under Category I for topically applied products. In vitro and in vivo efficacy studies with up to date sampling techniques, including the use of neutralizers, are required.

REFERENCES

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HEXYLRESORCINOL

8. The Panel has reviewed the submission regarding the safety and effectiveness of hexylresorcinol. The few animal toxicity studies submitted as summaries indicate a low order of toxicity (Ref. 1). However, no information has been submitted regarding dermal or opthalmic toxicity or absorption and blood levels attained after application to the intact or abraded skin or mucous membranes.

Hexylresorcinol has a history of use as an oral anthelminthic in humans. In these cases the dose used in children has been 600–800 mg. and in adults 1000 mg. Ref. 2 and 4) without systemic toxicity. However, irritation and ulceration of the oral and gastrointestinal mucosa have been reported from these high doses (Ref. 2 and 4).

During its long history of use, there have been a few reports of dermatitis and allergic reactions following the topical application of hexylresorcinol to skin (Ref. 3, 4, 5) and of irritation of the oral mucosa from the use of cough drops and toothpaste containing hexylresorcinol (Ref. 3 and 4). However, the Panel is of the opinion that hexylresorcinol does not present a known hazard to the general public from use as a topical preparation.

Data have been submitted demonstrating in vitro effectiveness using techniques available some years ago. Neutralizers for antiseptic testing were not in general use at the time these studies were performed and their use was often ignored. Newer testing techniques are currently available and should be used in further studies to determine the in vitro activity of this ingredient. Adequate data to demonstrate clinical or in vivo effectiveness or to substantiate label claims have not been submitted.

The Panel has reviewed rather extensive reports of the oral administration of hexylresorcinol to humans with other accompanying animal toxicity data (Ref. 1) and has concluded that topical application, even where absorption might occur at high levels, is safe. The area in which data are lacking concerns the in vitro and in vivo effectiveness of the ingredient and of formulations containing it. Before hexylresorcinol can be moved to Category I for other product categories, these effectiveness data must be generated using modern testing procedures and skin sampling techniques, including the use of neutralizers.

REFERENCES

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(5) Oster, K. A., "Chemotherapy of Bacterial Infections 1: Antiseptics and Germicides," *"Drill's Pharmacology in Medicine,"* 4th Ed., Edited by DiPalma, J. R., McGraw-Hill, New York, 1971.

TRIPLE DYE

9. The OTC Antimicrobial Panel has thoroughly reviewed the published literature and has listened to additional testimony from interested parties concerning the safety and effectiveness of the combination of dyes (crystal violet, 2.29 g; brilliant green, 2.29g and proflavine hemisulfate, 1.14 g and sufficient water to make 1000 ml) known as Triple Dye.

The Panel has reviewed the use of Triple Dye for the treatment of the umbilicus prior to the introduction of hexachlorophene, and has reviewed its recent use in the prevention of staphylococcal colonization of neonates as a possible replacement for hexachlorophene. It is the opinion of the Panel that the evidence indicates that a single application of triple dye to the umbilicus is effective in the reduction of staphylococcal colonization in infants in the hospital nursery (Ref. 1, 2, 3 and 4). Confirmatory studies would be desirable.

It is also the opinion of the Panel that additional safety data including the degree of percutaneous absorption and concomitant toxicity of the combination is required.

Additional effectiveness data are needed to determine the duration of protection following a single application of dye. The difficulty in the establishment of effectiveness by skin sampling for staphylococcal colonization is increased by the presence of small quantities of transferred dye in the culture medium used to isolate staphylococci and must be considered in further tests of effectiveness.

It is the opinion of the Panel that the data reviewed were not sufficient to permit final classification of triple dye.

The substantiation for this view is found in OTC Volume 020144 (Ref. 1) and in articles by Pildes et al. (Ref. 2), Jellard (Ref. 3), Hardyment et al. (Ref. 4) and Huntingford et al. (Ref. 5).

In summary the Panel reviewed this combination of antibacterial dyes primarily as a result of their concern with the toxicity of hexachlorophene. The application of triple dye to the umbilicus is a potential replacement for hexachlorophene bathing of infants in the nursery to reduce staphylococcal colonization. They have reviewed the literature and available information concerning the toxicity. Further data on the absorption, possible carcinogenicity of the dye ingredients and corroborative efficacy data should be generated before triple dye can be placed in Category I for this limited indication.

REFERENCES

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(2) Pildes, R. S., R. S. Ramamurthy and D. Vidyasagar, "Effect of 'Triple Dye' on Staphylococcal Colonization in the Neonate," Draft of paper submitted for publication is included in OTC Volume 020186.

(3) Jellard, J., "Umbilical Cord as Reservoir of Infection in Maternity Hospital," *British Medical Journal*, I:925–928, 1957.

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LABELING

The Panel has determined that labeling claims not identified in Category I or Category II of this document continue to be used until 1 year after publication of the final monograph in the FEDERAL REGISTER providing the manufacturer or distributor of the product promptly undertakes adequate testing to support such statements.

GUIDELINES FOR TESTING

After exhaustive review of the data submitted for antimicrobial ingredients in soaps, surgical scrubs, skin washes, skin cleansers, and first-aid products, the Panel has developed guidelines for safety and effectiveness studies. These guidelines should be followed to develop data for specific ingredients where the information does not currently exist.

The Panel recognizes that antimicrobial use ranges from total body exposure to application on small areas of the body. This may extend from daily, repeated to intermittent, occasional application. The Panel also recognizes that the list of products may include solids, liquids, creams, powders, and aerosols, formulated with various chemical excipients.

The guidelines which follow were developed primarily for antimicrobial agents applied to the entire body surface.

Appropriate tests from the guidelines should be chosen to reflect adequately the intended use of the product containing the antimicrobial agent. Aerosols, for example, should include inhalation tests.

The Panel recognizes that there may be honest disagreement among scientists as to the most appropriate design of a protocol for many of the tests required to provide the data on which a final determination of category can reasonably be made. In this event, conferences with expert consultants and with representatives of the Food and Drug Administration are recommended. The Panel also recognizes that they have recommended studies in areas and with specified details for which precedents are not common.

GUIDELINE FOR SAFETY AND EFFICACY TESTING OF OTC TOPICAL ANTIMICROBIALS

Preparations applied to the skin for the purpose of reducing microbial counts or to effect control of infection may be applied to limited areas or to entire body surfaces. The following points are suggested as guidelines for the safety and effectiveness evaluation of topically applied chemicals. Since some products containing an antimicrobial agent(s) may be employed only over a limited surface area and/or for a limited time, all of the specific tests in the guidelines list (as well as others) may not be required.

Since topical products frequently have a considerable placebo effect, there must be some demonstration that the formulated product is better than the vehicle alone. Testing of the complete formulation for effectiveness and safety will be required to judge the importance of the vehicle in the release of the active ingredient as well as the influence of formulation on aspects of effectiveness and safety.

A. *Safety.* (Tests below to be performed on suitable animals and then on humans when applicable, appropriate and ethically feasible.)

1. *Topical (skin).* Determine:

a. Primary irritation potential following acute and subacute exposure. Special attention devoted to eyes, mucous membranes, and genitalia.

b. Allergic contact dermatitis potential following acute and subacute exposure.

c. Photosensitivity potential (phototoxic and photoallergenic). Tests to be conducted in appropriate age bracket in men and women and in sufficient numbers to determine safety.

d. Effect on wound healing.

e. Effect on skin pigmentation.

f. Effect on total skin flora to insure no detrimental over-growth of a particular bacterial or fungal species.

g. Substantivity or accumulation in or on the skin.

NOTE: The above tests should be performed using the chemical in pure form and in the final complete formulation to judge the effect of vehicle in the release of active ingredient(s).

2. *Systemic.* Determine:

a. The adequacy of or development of chemical analysis and/or bioassay techniques for the detection of the chemical and metabolites in biological tissues and secretions is essential.

b. Degree of absorption (blood level) through intact and abraded (damaged, diseased) skin and mucous membrane after acute and subchronic exposure and where appropriate, chronic exposure. If the product is an aerosol, adequate inhalation studies should be conducted.

c. The target organ(s) for toxicity effects via oral, topical and/or parenteral routes. Relate toxicity to blood levels of chemical agent. Determine the "no-effect" and "effect" level in the same species and same study.

d. The LD_{50}, highest dose killing no animals and lowest dose killing all the test animals by oral and topical routes, if possible.

e. Tissue distribution, metabolic rates, metabolic fate, and rate and routes of excretion.

f. Teratogenic, mutagenic, carcinogenic, and reproductive effects.

NOTE: The above tests should be performed using the chemical in pure form and in the final complete formulation to judge the effect of vehicle in the release of the active ingredient(s).

B. *Effectiveness.* The Panel has established by its definition of a skin antiseptic that only this product category requires controlled clinical studies to establish efficacy. The Panel accepts that in the definition and/or historical use of other product categories, the reduction of the normal flora, both transient and resident, has been sufficiently supported as an added benefit in all other products where antimicrobials are included in the formulation.

In the context of all of the definitions the concept that the products must be safe and non-irritating is expressed.

Testing of the irritation of topically applied products can be performed by accepted procedures.

Since product categories which did not exist previously have been defined by the Panel, there will be a need to develop adequate testing procedures in some of these new areas. There is particularly need to develop in vivo procedures for the newly defined products. The guidelines which follow are designed as an outline of suggested procedures which the Panel feels will characterize an antimicrobial product or ingredient. Certainly, the Panel recognizes that changes and additions will need to be made as newer techniques become accepted.

1. *In vitro.* a. Develop techniques for adequate neutralization of the chemical agent, before testing its antimicrobial[2] spectrum. Insure that the neutralizer is not toxic to the test organisms.

b. Determine the antimicrobial spectrum of the chemical(s) alone and in its final formulation. Use both standard cultures and recently isolated strains of each species. Cultures representing normal skin flora and skin pathogens should be selected.

The following outline has been prepared to serve as a basic guide for the in vitro characterization of the activity of an antimicrobial ingredient:

c. Determine the minimal inhibitory concentration (MIC) under standard conditions against standard organisms with known phenol coefficients and susceptibilities to other antimicrobial chemicals.

A series of recently isolated mesophilic strains including members of the normal flora and cutaneous pathogens (100 isolates) should be selected. Representatives of the following groups should be included.

NOTE: Special media and/or environmental conditions may be required:

1. Staphylococci-5 groups.
2. Micrococci.
3. Pyogenic Streptococci (Groups A, C, D should be included.)
4. Diphtheroids-Lipophilic, Non-Lipophilic, Anaerobic (*Propionibacterium*).
5. Gram negative enteric bacilli:

i. *Escherichia, Enterobacter, Klebsiella, Proteus,* and *Serratia* should be included.

ii. *Pseudomonas aeruginosa* and *Pseudomonas* species.

6. *Neisseria* species.
7. Aerobic Spore-Formers.
8. Atypical mycobacteria—fast growing strains.
9. Fungi—Yeast-like species. *Pityrosporum ovale, Pityrosporum orbiculare, Candida albicans, Candida parapsilosis,* and *Torulopsis glabrata.*
10. Selected Filamentous Dermatophytic species.
11. Viruses—hydrophilic, lipophilic.

d. Determine possible development of resistance to the chemical. Sublethal levels of the active ingredient(s) can be incorporated into the culture medium for an extended series of exposures. Use standard methods to determine the emergence of resistance.

e. Phenol coefficient

Use standard procedure with and without a specific neutralizer. If none is available, use 10 percent serum. Second subcultures, to determine the viability of the strain, should be made.

f. Other tests for antimicrobial effectiveness—data substantiating antimicrobial action by standard procedures, such as the Sykes-Kelsey procedure, and others where applicable, should be used. It would be advisable to include in the in vitro test a chemical(s) with recognized antimicrobial activity, for purposes of comparison.

2. In vivo.

a. Appropriate tests approximating use conditions for the clinical evaluation of each label claim of the formulated product should be carried out. Some of these tests have been described.

1. Quantitative and qualitative estimation of the skin flora, both transient and resident.
2. Glove juice procedure.
3. Cade handwashing test.
4. Quinn handwashing test.
5. Skin-stripping or cup-scrubbing techniques should be used.

b. Feasible methods of sampling microbial communities in several different areas of the body, such as axilla, groin, feet and hands, are necessary so that the ecological effects of use of the product can be determined. This should include records, not only of alteration in total numbers, but of qualitative changes (such as dominance of a different type or change in antimicrobial resistance) in the residual cutaneous populations.

c. Determine the minimal concentration of the chemical necessary to produce the results named in the label claim(s).

Details of some of the specific tests referred to in the Guidelines can be found in Ref. 1 through 4.

REFERENCES

(1) Hugo, W. B., *"Inhibition and Destruction of the Microbial Cell,"* Academic Press, New York, 1971.

(2) Kelsey, J. C. and G. Sykes, "A New Test for the Assessment of Disinfectants with Particular Reference to Their Use in Hospitals," *Pharmaceutical Journal,* 202:607–609, 1969.

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PRINCIPLES OF CLINICAL EFFECTIVENESS STUDIES

In general, the Panel recommends that the principles specified in 21 CFR 130.12 (a) (5) (ii) be included as essential for adequate and well controlled clinical investigations. The reader is also referred to additional clinical testing guidelines (Ref. 1). The following specific recommendations are made to emphasize their importance in conducting clinical trials for products in this class.

A precise statement of the research goals and objectives; definitions of the disease state to be studied. Examples: To determine if "X" product reduces the incidence of superficial skin infections (specify type) if applied (specify how), to reduce morbidity or cure "Y" disease.

Since the Panel is aware of the difficulty in conducting this research, it might be preferable to conduct such studies in a controlled laboratory setting rather than awaiting the spontaneous occurrence of disease.

The allocation of the subjects to treated and control groups so that bias in assignment is avoided (randomization or other suitable method). Demonstration of comparability of control group (analysis by age, sex, previous medical history, etc.).

Because of the considerable "placebo effect" of topical medication, several principles should be incorporated, whenever possible, in clinical trials of topically applied formulations.

a. Control groups should receive treatment of either inert vehicles of "next-best" therapy, identical in appearance, odor and consistency as the test medication;

b. A double-blind procedure should be employed to minimize bias in reporting of results.

Precise criteria for inclusion or exclusion from study (clinical judgment; other diseases; social class, etc.). Verification of diagnosis of disease to be treated.

Definition of outcome response variables (improvement: How measured? cure: How determined?). Are these objective or subjective measures?

Study design: Is it blinded? Large enough sample to detect a difference? Cross-over, etc.? The rationale for the design.

Completeness of the study (how are missing data, dropouts, etc., treated).

Data summarization and statistical analyses. Are the appropriate tests of significance used? Are tables clear and properly labeled? Are conclusions justified by the data?

Basic principles applicable to clinical studies in general and references used in the development of these guidelines can be found in Ref. 2 through 4.

REFERENCES

(1) "Guidelines for Clinical Testing of Topical Anti-infective Drugs" developed by the Food and Drug Administration and the Pharmaceutical Manufacturers Association is included in OTC Volume 020186. Copies are available from the Freedom of Information Officer, Food and Drug Administration, Bureau of Drugs, 5600 Fishers Lane, Rockville, Maryland 20852.

(2) Burdette, W. J. and E. A. Gehan, *"Planning and Analysis of Clinical Studies,"* Charles C. Thomas, Springfield, 1970.

(3) Hill, A. B., *"Statistical Methods in Clinical and Preventive Medicine,"* E. and S. Livingstone, London, 1962.

(4) Witts, L. J., *"Medical Surveys and Clinical Trials,"* 2nd Ed., Oxford University Press, New York, 1964.

SPECIFIC PROTOCOLS RECOMMENDED BY THE PANEL

In the course of its deliberations, the Panel has made certain suggestions and recommended the development of specific protocols. Some of these comments and protocols follow.

1. *Determination of skin flora (Other than on the hands).* The development of sampling techniques in recent years now

[2] "Antimicrobial" is defined as antibacterial, antiviral, antifungal and antiprotozoal.

permits a more accurate determination of the microbial flora of various parts of the body surface.

Of the techniques which have been developed, Updegraff (Ref. 1) has described a reliable procedure for the determination of qualitative changes in the microbial skin flora. This technique consists of skin stripping of microorganisms using cellophane tape. The skin can be stripped in consecutive layers followed by culturing and identification of organisms removed by consecutive strippings.

Williamson (Ref. 2) and Pachtman, et al. (Ref. 3) have described cup procedures utilizing a scrubbing solution placed in the cup which is attached to the skin. Some means of agitation of the liquid for more efficient removal is used.

The use of one or more of these techniques allows the determination of the number of microorganisms per square cm. It will also allow the determination of the type of organisms residing on various areas of the skin as well as the assessment of the effect of the long-term use of antimicrobials on the normal flora.

A potential benefit from the presence of the normal diphtheroid population of the skin has been a point of speculation. There are indications (Ref. 4) that these organisms may discourage the development of cutaneous infection by pathogens. If changes and shifts in population occur after the repeated use of antimicrobial-containing products, then it must at least be known that the changes are occurring.

In actual practice, the volar aspect of the forearm and the small of the back have been selected as areas for study of the flora because of ease of sampling and greater uniformity in type of flora. It is suggested that individuals with a high microbial skin count be selected as subjects for studies in which there is to be a determination of change in the number of microorganisms in any given area of the body surface. Such individuals will reasonably show changes in various elements of the flora more easily than those with low carriage or in those who lack certain types of organisms.

In studies where quantitative changes are determined, the investigator should consider the fact that the count data should be evaluated with appropriate statistical procedures and models to deal with high variability.

REFERENCES

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(2) Williamson, P., "Quantitative Estimation of Cutaneous Bacteria," *"Skin Bacteria and Their Role in Infection,"* Edited by Maibach, H. I. and G. Hildick-Smith, McGraw-Hill, New York, 1965.

(3) Pachtman, E. A., E. E. Vicher and M. J. Brunner, "The Bacteriologic Flora in Seborrheic Dermatitis," *The Journal of Investigative Dermatology*, 22:389–396, 1954.

(4) OTC Antimicrobial I Panel Summary Minutes for the September 14, 1972 meeting.

2. *Isolation of gram negative and other organisms from the skin.* Gram-negative bacteria do not occur as residents of the skin of all individuals, and when present may be found only as small localized populations. They occur most frequently in moist areas such as the axilla, the peri-anal region and the toe-webs. It has however been shown by Taplin (Ref. 1), and Amonette and Rosenberg (Ref. 2) that the repeated use of preparations containing antimicrobial substances may lead to a change in the composition of the cutaneous community so that gram negative species, or even yeasts may become dominant. This may have very serious consequences as cutaneous or even systemic infections may develop. It is therefore insufficient to study only the effects of long-term repeated use of an antimicrobial product on the total numbers of microorganisms on the skin. It is essential to know to what extent reduction of numbers is selective, and to study the composition of the residual skin population. Special attention should be given to determining whether repeated use of the product leads to a relative increase of gram negative bacteria or yeasts in the total population.

The Panel suggests the use of the following procedures as a means of facilitating such studies.

A. A preliminary investigation of groups of individuals should be made so that carriers of gram negative organisms can be identified. To find these carriers, samples should be taken from the forehead, axilla, groin and toe-webs as well as from hands and back. The groups of subjects selected for the testing of the preparation should include the gram negative carriers previously identified.

B. Sampling techniques which can provide reasonably reproducible results should be employed. These have been listed in the general guidelines. The sample taken from the skin should be sufficiently large to permit the quantitative inoculation of several different solid media.

C. The following types of media should be inoculated with a measured volume of the sample:

1. A nonselective medium such as blood-agar or TSA (Trypticase Soy Agar).

2. Selective media appropriate for the isolation of microorganisms of special importance as skin inhabitants:

a. EMB (Eosin-Methylene Blue) or MacConkey Agar for coliform organisms.

b. Irgasan (Triclosan)—containing agar for *Pseudomonas* species.

c. *Staphylococcus* isolation agar, e.g., Staph 110.

d. Crystal Violet-Blood Agar for beta-haemolytic streptococci.

e. DTM (Dermatophyte Test Medium) for *Candida* and dermatophytes described by Taplin et al. (Ref. 3) and Rebell and Taplin (Ref. 4).

D. While quantitative estimates of the different types of organisms composing the cutaneous populations may be obtained from these primary cultures, it may be necessary to study individual isolates in much further detail before they can be identified and the implication of their presence assessed.

The Panel is fully aware of the difficulties involved in the examination and identification of microorganisms living on the human skin. It would welcome the development of new sampling techniques and media especially selective for cutaneous microbial strains. Elaboration and improvement of the methods currently used in investigation of cutaneous ecology is urgently required.

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(2) Amonette, R. A. and W. E. Rosenberg, "Infection of Toe Webs by Gram-Negative Bacteria," *Archives of Dermatology*, 107: 71–73, 1973.

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(4) Rebell, G. and D. Taplin, *"Dermatophytes, Their Recognition and Identification,"* University of Miami Press, Coral Gables, 1970.

3. *Effectiveness testing of a surgical hand scrub (glove juice test).* Panel members working with Food and Drug Administration personnel and other microbiologists (Ref. 6 and 9) recommended the following which is required by the Food and Drug Administration. The test described must be performed to support the efficacy of a product labeled as a surgical hand scrub.

Introduction. The determination of the microbial counts found in the accumulated fluid in the surgeon's gloves has been suggested in the literature as a method for the determination of the efficacy of surgical scrub products. The use of routine hand-washing procedures derived from the Price Test described in 1938 (Ref. 1) have their place but the results of these tests are easily manipulated by changes in the routine, timing, and recovery procedures. The development of improved sampling (sampling solution) procedures and recovery techniques (neutralizers) by Williamson (Ref. 2), Ulrich (Ref. 3) and Engley and Dey (Ref. 4) has greatly improved the reliability of skin sampling data. An effectiveness test which more closely simulates the actual procedures carried out by the surgeon is desirable and necessary.

This protocol is meant to be a guideline for performing tests to support claims of effectiveness as a surgical hand scrub. It will undoubtedly be modified with experience.

Criteria for subject selection. 1. Mixed male and female. Race should be recorded.

2. Adults.

3. Subjects will vary greatly in the number of microorganisms carried on the skin. Subjects with a high hand count as measured by sampling with the glove juice procedure should be used for the test. Counts should be in the range from 1.5×10^6 to 4×10^6 per hand.

4. Medication. Subject receiving antibiotics or taking oral contraceptives should be excluded from the test.

5. Thirty (30) subjects per test.

Pre-test period. 2 weeks.

The subjects for this test should not use any products containing antimicrobials for at least 2 weeks prior to the test. This restriction includes antimicrobial antiperspirants and deodorants, shampoos, creams, lotions, soaps, or powders. Subjects receiving antibiotic therapy or taking oral contraceptives should be disqualified.

Subjects should be issued rubber gloves to be worn during their daily routine when they come in contact with detergents, acids, bases or solvents.

Gloves for test. Gloves should be washed with sterile distilled water before use and applied wet. Gloves which are pre-powdered should be carefully washed free of powder as many of these powders contain antimicrobials.

Baseline period and sampling. The baseline period should be one week following the two weeks of the pre-test period. The baseline counts should begin on day one of the baseline period. This initial count is a screen to determine eligibility.

The day one count is also one count to be included for the mean baseline count. The counting procedure should be performed on day seven and also on either day three or five for a total of three estimations of the baseline count.

The baseline counts should be performed using exactly the same sampling and recovery techniques used for the test products under the testing procedure. This information will also be used to provide evidence to assess the assumption that the right and left hand gave comparable results.

Both hands should be sampled for the baseline count. Subjects should not wash prior to the counting procedure on the day of the test.

Baseline procedure is as follows: Hands including ⅔ of the forearm are washed for 30 seconds with Camay soap and sterile distilled water at 35–40° C. The excess water is shaken from the hands and the gloves are donned with the hands wet. Sampling solution (see Appendix) is added to the gloves (volume of sampling solution should remain constant for all tests). The glove is held closed at the wrist by the subject while an attendant massages the hand for one minute. A measured volume is withdrawn for the count.

Testing Procedure

Scrubbing procedure. The scrubbing procedure should be exactly as directed on the label of the product being tested, including the use of nail cleaner and/or a brush if indicated. The hand and ⅔ of the forearm should be scrubbed.

Sampling technique and times. After the scrub is performed, loose-fitting surgeon's or examining gloves are donned. Leave the hands wet by shaking off excess water when the gloves are donned. Immediately, the designated control hand is sampled for the one minute count as follows: Sampling solution containing buffer and surfactant is added to the glove, the hand is massaged for one minute, and a measured sample removed for plating. The volume of the sampling solution added to the glove should be kept constant for all tests. The fluid should be shaken vigorously prior to dilution or culturing. If diluent is used, neutralizer should be added to dilution blanks.

The glove is to remain on the other hand for the duration of the time of the test. It is suggested that at least 1, 2, 3, 4, 5, and 6 hours post scrub should be tested.

The times for which a glove remains on one of the hands after scrub should be allocated by random selection among the subjects in groups of five. This procedure is performed on day one and day two of the test period. The procedure should be repeated on day five after scrubbing with the product according to directions two additional times on day two and three times per day on day three and four at one-hour intervals. One scrub should be performed on day five and the gloves allowed to remain on the left hand for 1, 2, 3, 4, 5, or 6 hours.

The number of subjects used for the test should be 30 with randomization into six groups (n=five per group) corresponding to one hour, two hours, three hours, four hours, five hours and six hours. The allocation of subjects to groups remains constant after initial randomization.

Recovery media. A medium containing a neutralizer specific for the antimicrobial being tested must be used. Media which have been used in the past include: Letheen and Trypticase Soy Agar with Tween 80 and serum added.

The neutralizing system used for antimicrobial agents must be tested, and the data from the tests submitted, to show that the system is adequate. The neutralizer should not be toxic to cells and must be effective in neutralizing the specific chemical. This data must be submitted.

The cultures should be incubated at 30±2° C. for 48–72 hours. If culturing for specific organisms, such as fungi or anaerobes, is undertaken, appropriate culturing procedures should be instituted.

Duplicate plates have been routinely used for plating in the past. Because of the inherent variability in counts and the presence of clumps of cells from skin sampling, it is suggested that at least triplicate plating be used. A larger number may be required, depending on the variability. The counts should be reported as count per hand.

There are variations of this procedure in use. For instance, instead of sampling directly from the glove, the glove is removed, turned inside out into stripping fluid, and the hand rinsed with sampling solution as well. If variations of this test are to be used, the protocol should be checked with Food and Drug Administration personnel first.

Data handling—design—statistical aspects. It is assumed that there are no right versus left hand differences in microbial count. It is known that microbial handedness (a difference in count between hands) exists; however, there is apparently no relationship to whether the subject is left or right handed. The possible difference in count should be compensated for with the initial random allocation of subjects.

This will be tested using the baseline count to validate assumptions about the influence of handedness. It is necessary, therefore, to keep data for the left and right hand distinct.

The assignment of hands is as follows:

1. Right hand at 1 minute as observation of reduction from baseline (right hand baseline) on all subjects (30 subjects).

The objective of the design will be to test as follows:

a. Test the $\log_{10}$ reduction from baseline 1 minute after scrubbing with fast-acting broad spectrum antimicrobials.

b. Test the initial $\log_{10}$ reduction from baseline one minute after scrubbing with a substantative antimicrobial.

c. Test the $\log_{10}$ reduction from baseline 1 minute after scrubbing following 3 days with three consecutive scrubs per day performed at one-hour intervals.

Statistical Aspects

a. A test of the assumption that the agent produces a given $\log_{10}$ reduction, such as 1-$\log_{10}$, 2-$\log_{10}$, or 3-$\log_{10}$, reduction will be made using the data from the one minute result from the right hand compared to the average baseline (right hand baseline). A method like a paired t-test could be used.

b. Left hand at a time designated by random assignment to one of six time periods (five subjects in each of six groups) will be compared to left hand baseline.

The objective here will be to characterize the trend (in microbial growth) with time up to six hours. It is desirable that the count, over six hours, with fast-acting, broad-spectrum antimicrobials not exceed the baseline. It is expected that the count will not exceed baseline in six hours in the testing of substantive antimicrobials.

Analysis

The analyses will be performed first on each replication. There is replication of the entire test on day two and on day five after three consecutive washes at hourly intervals on day three, four, and five. Use the original group assignments of subjects observed for the same time periods as determined by random allocation.

Tests of trends may be done using either an orthogonal procedure or some suitable regression method. A combined analysis using the results of the three replications is possible using an appropriate analysis of variance technique. For example; an analysis of variance on the total set of experimental results using the model described on page 519 ("Statistical Principles in Experimental Design," B. J. Winer, McGraw-Hill Book Company, 1961) where hours correspond to factor A and replications correspond to

factor B. Baseline could be introduced as a covariant. Tests of trends using the orthogonal procedures will be employed.

APPENDIX

1. *Sampling solution.* (Williamson, Ref. 2).
Triton X-100—0.1 percent in 0.075 M phosphate buffer.
pH—7.9.

2. *Sampling fluid.* (Peterson, Ref. 6 and 9).
Potassium phosphate (monobasic)—0.4 g.
Sodium phosphate (dibasic)—10.1 g.
Triton X-100—1.8 g.
Distilled water—1 liter.
Final pH=7.8.

The Glove Juice Test is required to show the effectiveness of a product to be labeled for use as a surgical hand scrub. Other handwashing procedures should also be performed if there are indications for personnel handwashing. The two preferred procedures are the Cade and the Quinn handwashing procedures. The details of these tests are published in the literature. Following are some comments about these procedures are offered.

4. *Effectiveness testing of handwashing products*—a. *Comments applicable to all handwashing testing procedures.* The numbers of micro-organisms present before and after scrubbing with various formulations have been enumerated and reported in the literature over the years. One thing which has not been reported is the identity of the micro-organisms removed and those which remain. The spectrum of micro-organisms against which any one of the antimicrobial agents acts is variable.

The effect of the prolonged use of such products on the normal human skin flora is essential information for all antimicrobials designed for repeated use.

There are indications that replacement populations may indeed occur if certain micro-organisms are removed or suppressed (Ref. 7 and 8). In addition it is becoming evident that the normal flora of the skin may protect against skin infections.

The comments concerning the use of multiple plates in the culturing procedures as well as the evaluation of specific neutralizers for use in the testing of antimicrobial agents apply to all in vivo testing.

b. *Cade handwashing procedure.* This test has been described by Cade (Ref. 5) and is an adaptation of the Price (1938) handwashing test.

This procedure has been widely used to estimate effectiveness. It has also been widely adapted.

It has been the practice to use 6–10 subjects for basin tests. The count data are utilized to compare the mean baseline count with the count after use of the test product. The comparison is most often made as "percent reduction". This has been the criteria of effectiveness, frequently without further analysis.

If one considers the inherent variation, the number of subjects is not at all adequate. Other, more sophisticated analysis, such as analysis of covariance and hypothesis testing of whether the reduction meets an established criterion, is required, rather than simple and possibly misleading percent reduction. Subjects must refrain from the use of all products containing antimicrobials for two weeks prior to the test. The period for establishment of the baseline count for subjects in the test should be at least two weeks. Sampling for baseline counts should be toward the end of the baseline control period and should be done at least three times. Subjects taking antibiotics or oral contraceptives should be disqualified.

A non-antimicrobial soap should be used for washing when microbial counts are to be done.

c. *Quinn split-use test.* This test has been described as a modification of the Cade Test (Quinn, 1954). The primary difference is that one hand is used as the control for the test hand instead of using an established baseline count as the control.

The comments made previously concerning the number of subjects in the test apply here.

The comments concerning subjects also apply. There is normally no baseline count established. Subjects should refrain from the use of products containing antimicrobials for at least two weeks prior to the test (pre-test period) since many ingredients are substantive. The Panel recommends the establishment of a baseline count during the week following the pre-test period as a good addition to this testing procedure.

d. *Testing health-care personnel handwashing product.* Since the result expected from the use of this type of product is the reduction of the transient flora acquired as a result of patient care or as a part of hospital routine, the testing must involve the artificial contamination of the hands and forearms. This procedure can be executed by dipping the hands into a liquid culture with at least 10^8 organisms per ml. and allowing one minute before proceeding. The artificial contamination of the hands may also be produced by handling heavily contaminated materials to simulate actual practice.

The product under test should be used according to the directions on the label. Since these products are designed to be used with multiple replication, the effectiveness testing procedure of hand contamination and washing followed by evaluation of the count of the contaminating organisms should be done at least 25 times in succession. Some period of time should be allowed between repeats. Evaluation of the count on the hands can be done approximately every 5 washes.

In order to reliably carry out this test, a marker strain of a microorganism should be selected for use which is not part of the normal flora and which may be easily identified on culture plates. Two organisms frequently selected for this purpose are *Serratia marcescens* (pigmented strain) and *Bacillus subtilis* var. *niger* (strain globigii), Detrich isolate—ATCC 9372.

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5. *Effectiveness testing of a patient pre-operative skin preparation.* The historical use and basic effectiveness requirements are presented under the general discussion of efficacy of pre-operative skin preparations. The reader is referred to the definition and discussion of the product.

There are no established protocols for the testing of this category of products. From the defined use of the product, the antimicrobial as well as the formulated product, should be tested for basic in vitro data to establish its broad-spectrum activity. (See Guidelines).

The in vivo efficacy testing procedures should utilize the skin sampling procedures in the Guidelines and in the discussion of efficacy. Since any given area of skin surface can be tested, the control area can be the same location on the other half of the same subject (bilateral paired comparison).

Since the definition states that rapid activity is required, the time for testing activity should be 30 minutes maximum.

The baseline count on the control area matching the test area should be established using cup-scrubbing, tape stripping techniques or other appropriate sampling techniques. The same procedure should be used for skin area treated with the active produet. The test must be done using an adequate population and with sampling from skin areas on various parts of the body and certainly, including the genital areas.

It is essential that the sample from the skin be properly neutralized to inactivate active chemical carried over from the

skin. The neutralizer used must be tested for toxicity to cells and for efficacy as a neutralizer. The sample as well as the culture conditions must be adequate to determine the range of organisms which can be isolated from the skin. (See Guidelines for suggested media). A minimum of three-log reduction will be required to establish efficacy for a product labeled as a pre-operative skin preparation.

6. *Testing of a skin wound cleanser.* This product category has been established and defined by this Panel. The reader is referred to the definition and discussion of product category. Inherent in the definition is the concept of cleansing and removal of foreign material.

Absence of delay in wound healing must be established for a product in this category.

The Panel recognizes that the testing of delay in wound healing, particularly in human subjects, is difficult.

Animal models have been used with artificially contaminated wounds by some investigators (Ref. 1, 2 and 3). See Efficacy Discussion and Iodophor Statement.

There is a need for the development of procedures to determine whether topical products applied to minor skin wounds would delay healing in human subjects. Until adequate human testing procedures are available, data from animal models will be required to support safety of a product to be labeled as a skin wound cleanser.

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7. *Effectiveness testing of a skin wound protectant.* The reader is referred to the definition and discussion of a skin wound protectant. From the definition, a skin wound protectant must act as a physical barrier. The testing of barrier materials can be done with a model system and fluorescent particle challenge to the system with subsequent detection of the challenge particles on the other side of the barrier. A model for this challenge will have to be developed.

The second aspect of this definition to be tested is the lack of promotion of the growth of microorganisms. This characteristic can be tested first in an animal model system in which a wound is artificially produced in the animal skin. The extent of the microbial growth in such a system may be tested with various levels of microbial contamination added to the wounds. The growth or reduction of growth could be followed by appropriate skin sampling techniques performed in a time series after application of the test product. The growth may also be assessed by using an inoculum lower than the minimum infective dose of a pathogen for the animal followed by determination of infections in the treated animals.

Animal tests should be followed with human testing. At the current level of development of techniques, artificial contamination in humans cannot be recommended. However, a standard wound, such as that produced by a skin punch biopsy, may be used to test whether the product to be labeled as a skin wound protectant promotes microbial growth in a minor wound. Another approach in the production of an artificial injury for human testing which might be used is the repetitive skin stripping technique of Marples (Ref. 1). This procedure uses the repeated removal of skin layers with cellophane tape until the glistening layer is exposed. This minjor injury can reasonably be used for these testing purposes but would simulate only very minor wounds. Skin graft donor sites might also be used.

With any model selected for testing, particular attention should be given to testing the growth of anaerobic microorganisms where an occlusive system is used. It is expected that up-to-date techniques for the isolation and growth of anaerobes would be employed.

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Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 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, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that Subchapter D be amended, pursuant to the recommendations of the Advisory Review Panel on Over-the-Counter Topical Antimicrobial Drugs, by adding a new Part 333, effective 6 months after publication of the final monograph in the FEDERAL REGISTER, to read as follows:

PART 333—TOPICAL ANTIMICROBIAL PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Testing Procedures

Subpart D—Labeling

AUTHORITY: Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1055–56 as amended by 72 Stat. 919 and 72 Stat. 948; (21 U.S.C. 321, 352, 355, 371), and Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243, as amended; 5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 333.1 Scope.

An over-the-counter antimicrobial product in a form suitable for topical use is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 333.3 Definitions.

For topical preparations when applied at acceptable use concentrations (the dilution recommended for use as distinguished from marketed concentrates) as used in this part:

(a) *Antimicrobial soap.* A soap containing an active ingredient with in vitro and in vivo activity against skin microorganisms.

(b) *Health-care personnel handwash.* A safe, nonirritating preparation designed for frequent use which reduces the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying. If the preparation contains an antimicrobial agent, it should be broad-spectrum, fast-acting, and if possible, persistent.

(c) *Patient pre-operative skin preparation.* A safe, fast-acting, broad-spectrum antimicrobial-containing preparation which significantly reduces the number of micro-organisms on intact skin.

(d) *Skin antiseptic.* A safe, nonirritating, antimicrobial - containing preparation which prevents overt skin infection. Claims stating or implying an effect against micro-organisms must be supported by controlled human studies which demonstrate prevention of infection.

(e) *Skin wound cleanser.* A safe, nonirritating, liquid preparation (or product to be used with water) which assists in the removal of foreign material from small superficial wounds and does not delay wound healing.

(f) *Skin wound protectant.* A safe, non-irritating preparation applied to small cleansed wounds which provides a protective (physical and/or chemical) barrier and neither delays healing nor favors the growth of micro-organisms.

(g) *Surgical hand scrub.* A safe, non-irritating antimicrobial-containing preparation which significantly reduces the number of micro-organisms on the intact skin. A surgical hand scrub should

be broad-spectrum, fast-acting, and persistent.

Subpart B—Active Ingredients

§ 333.30 Patient pre-operative skin preparation.

(a) *Active ingredient.* The active ingredient of the product consists of the following within the maximum dosage limit established:

(1) *Tincture of iodine.* Iodine tincture contains not less than 1.8 grams and not more than 2.2 grams of iodine (I), and not less than 2.1 grams and not more than 2.6 grams of sodium iodide (NaI) in each 100 ml. of 44–50 percent ethyl alcohol or an appropriate denatured alcohol.

§ 333.40 Skin wound cleanser.

(a) *Active ingredients.* The active ingredients of the product consists of one or more of the following within any maximum dosage limit established:

(1) *Quaternary ammonium containing active ingredients.* Quaternary ammonium compounds (as Benzalkonium chloride, Benzethonium chloride and Methylbenzethonium chloride) limited to a use concentration not greater than 1/750. All preservative systems included in any such formulation must be tested according to the procedure described in The United States Pharmacopeia XVIII (page 846).

(2) *Hexylresorcinol.* Hexylresorcinol limited to a use concentration not greater than 1/1000.

Subpart C—Testing Procedures

§ 333.60 Preservative testing.

All antimicrobial ingredients used singly or as part of a preservative system for a topical product identified in § 333.3 shall be tested to establish the minimum effective preservative concentration for each product formulation. Determine the minimum effective preservative concentration according to the procedures described in the United States Pharmacopeia XVIII (page 845). The resulting data shall be submitted to the Food and Drug Administration for approval prior to use.

Subpart D—Labeling

§ 333.70 Antimicrobial soap.

The labeling of the product may contain any phrase in the definition of an antimicrobial soap established in § 333.3 (a). Labeling may also include the phrase(s): "Antimicrobial soap", "antibacterial soap", "reduces odor", "deodorant soap".

§ 333.75 Health-care personnel handwash.

The labeling of the product may contain any phrase in the definition of a health-care personnel handwash established in § 333.3(b). Labeling may also include the phrase(s): "Decreases bacteria on the skin", "reduces risk and/or chance of cross-infection", "recommended for repeated use".

§ 333.80 Patient pre-operative skin preparation.

(a) *Indications.* The labeling of the product may contain any phrase in the definition of a patient pre-operative skin preparation established in § 333.3(c). Labeling may also include the phrase(s): "kills microorganisms", "reduces the number of microorganisms in the treated area", "broadspectrum" (if such applies).

(b) *Warnings.* The labeling of the product contains the following warnings:

(1) "May delay healing or irritate broken skin".

(2) "Do not bandage".

(c) *Directions for use.* The labeling of the product contains the statement, "Apply to (paint) the operative site prior to surgery and remove immediately upon drying after application with 70 percent alcohol, or use as directed by a physician".

§ 333.85 Skin antiseptic.

(a) *Indications.* The labeling of the product may contain any phrase in the definition of a skin antiseptic established in § 333.3(d). Labeling may also include the phrase(s): "Prevents skin infection", "controls infection", "degerming", "kills germs", "bacteriostatic", "bactericidal", "reduces the risk of infection and cross-infection", "mircobiocidal", "first-aid product".

(b) *Directions for use.* The labeling of the product shall contain the statement, "Apply to affected area", and contain the recommended dosage for use, time interval (if any) and method by which the product shall be used to prevent overt skin infection for those particular organisms for which the product is generally recognized as safe and effective.

§ 333.90 Skin wound cleanser.

(a) *Indications.* The labeling of the product may contain any phrase in the definition of a skin wound cleanser established in § 333.3(e). Labeling may also include the phrase(s): "To clean superficial wounds", "wash superficial (small) wounds", "aid in removal of foreign materials such as dirt and debris", "first-aid product".

(b) *Warnings.* The labeling for Quaternary ammonium containing products contains the following warnings:

(1) For products marketed as concentrates: (i) "Caution: May cause eye irritation or eye damage unless diluted." (ii) Dilute before each use to avoid spoilage.

(2) "Use of solution with occlusive dressing is not advisable".

(c) *Directions for use.* The labeling of the product shall contain the statement, "Apply to affected area", and the recommended dosage for use and method by which the product shall be used to cleanse a small wound without further damage to the injured area.

§ 333.95 Skin wound protectant.

(a) *Indications.* The labeling of the product may contain any phrase in the definition of a skin wound protectant established in § 333.3(f) of this chapter. Labeling may also include the phrase(s): "Protects against contamination", "protectant", "protects wounds", "first-aid product".

(b) *Warnings.* The labeling of the product shall contain the following warnings:

(1) "Should not be used for large or deep wounds."

(2) "Should not be used for more than (time certain) days except upon advice and supervision of a physician."

(c) *Directions for use.* The labeling of the product shall contain the statement, "cleanse wound thoroughly before applying", and contain the recommended dosage and the method by which the product should be used.

§ 333.99 Surgical hand scrub.

The labeling of the product may contain any phrase in the definition of a surgical hand scrub established in § 333.3(g).

Interested persons are invited to submit their comments in writing (preferably in quintuplicate) regarding this proposal on or before November 12, 1974. Such comments should be addressed to the Office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before December 12, 1974. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: September 6, 1974.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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