21 CFR Part 356

[Docket No. 81N-0033]

Oral Health Care Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) oral health care drug products (products for use in the mouth and throat) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by August 23, 1982, and reply comments by September 22, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 14, 1979 a report on OTC oral health care drug products from the Advisory Review Panel on OTC Oral Cavity Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC oral health care drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

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

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC oral health care drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency notes that the Panel was charged to review the use of oral health care products as drugs but recognizes that many claims for these products historically have been considered cosmetic in nature. The Panel made specific recommendations on the cosmetic use of oral health care products, e.g., products containing pharmacologically active ingredients should not be used to achieve a cosmetic effect such as reduction of mouth odors. Also, there are numerous instances in which the Panel refers to the drug or cosmetic status of certain ingredients and claims. The Panel's recommendations and conclusions, if fully implemented, would result in extensive changes in the marketing of these products. As with other Oral Cavity Panel recommendations, the agency is deferring its decision with regard to the "drug versus cosmetic" status of OTC oral health care products until publication of the tentative final rule. This issue is important and requires careful study. The agency points out that is has previously discussed the "drug versus cosmetic" status of soaps containing antimicorbial ingredints in the rulemaking proceeding to establish a monograph for OTC topical antimicrobial drug products (39 FR 33103 and 43 FR 1212) and invites specific comments on this subject with regard to the oral health care products discussed in this document.

The agency's position on OTC oral health care drug products will be stated initially when the tentative final mongraph is published in the **Federal Register** as a proposed regulation. In the preamble to the tentative final monograph, the agency also will announce its initial determination whether the monograph is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the tentative final monograph is published. At that time FDA also will consider whether the monograph has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC oral health care drug products. Types of impact may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC oral health care drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC oral health care drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after June 24, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph had been established.

Accordingly this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the result of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler,* FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug produ cts that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug products that are subject to the monogrph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially intruduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monogroph regardless of the date the product was initally intruduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC oral cavity drug products was issued in the **Federal Register** of July 20, 1973 (38 FR 19444). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other then an 'active ingredient.' ")

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of those products:

Lawrence Cohen, Ph. D., M.D., D.D.S., Chairman
John Adriani, M.D. (appointed June 1974)
Roy C. Darlington, Ph. D.
Martin J. Goldberg, D.D.S.
Valerie Hurst, Ph. D.
Walter E. Loch, M.D.
Jeanne C. Sinkford, D.D.S. (resigned June 1974)

Arthur N. Bahn, Ph. D. (resigned July 1977 to accept a sabbatical appointment to the University of Utrecht for the period August 1977 to September 1978. He was reappointed to the Panel in December 1978. The vacancy created by his resignation was not filled.)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Mary Plaska served as the consumer liaison until she resigned in June 1977, and was followed by Sandra Zimmerman. Both were nominated by an ad hoc group of consumer organizations. Christopher H. Costello, Ph. D. (nominated by the Proprietary Association), served as an industry liaison throughout the Panel's deliberations. Kenneth W. Herrman, Ph. D. (nominated by the Cosmetic, Toiletry, and Fragrance Association), served as an industry liaison until February 1975, followed by Joseph Ambrozaitis, Ph. D., who served until June 1977, followed by Barry Gibberman, Ph. D., who served until February 1978.

Six nonvoting consultants provided assistance to the Panel:

William Bowen, D.D.S.
Neal W. Chilton, D.D.S., M.P.H.
Ralph B. D'Agostino, Ph. D.
Frank B. Engley, Ph. D.
Gordon Pledger, Ph. D.
Sigmund S. Socransky, Ph. D.

The following FDA employees assisted the Panel: John R. Carr, D.D.S., served as Executive Secretary. John T. McElroy, J.D., served as Panel Administrator. Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1977, followed by Cynthia Rutten, R.Ph., until December 1978, followed by Chester Trybus.

The Panel was first convened on February 26, 1974, in an organizational meeting. Working meetings were held on April 23, June 13 and 14, September 5 and 6, November 7 and 8, December 11 and 12, 1974; February 6 and 7, March 4 and 5, April 24 and 25, July 9 and 10, September 9 and 10, October 16 and 17, December 11 and 12, 1975; February 19 and 20, March 10 and 11, May 6 and 7, July 7 and 8, September 30 and October 1, December 9 and 10, 1976; February 23 and 24, April 12 and 13, June 9 and 10, July 20 and 21, 1977; June 6 and 7, October 17 and 18, 1978; January 4 and 5, August 14, and December 12, 13, and 14, 1979.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

The following individuals were given an opportunity to appear before the Panel, either at their own request or at the request of the Panel, to express their views on oral health care drug products:

Joseph F. Alexander, Ph. D.
Russell J. L. Allen, Ph. D.
Hazen J. Barron, D.D.S., Ph. D.
Robert Blank, Ph. D.
James F. Bosma, M.D.
William Bowen, D.D.S.
H. Alexander Bradford, M.S.
William Briner, Ph. D.
Richard C. Brogle, Ph. D.
Lewis P. Cancro, Ph. D.
Steven Carson, Ph. D.
Neal W. Chilton, D.D.S., M.P.H.
Sebastian G. Ciancio, D.D.S.
Joseph Clark, Ph. D.
John M. Clayton, Ph. D.
Eugene A. Conrad, Ph. D.
William E. Cooley, Ph. D.
Ralph B. D'Agostino, Ph. D.
Salvatore J. DeSalva, Ph. D.
Dennis G. Economy, M.D.
Jane F. Emele, Ph. D.
Frank B. Engley, Ph. D.
Raymond C. Erickson, Ph. D.
Malcolm H. Fine, M.D.
Arthur Flanagan, M.D.
Thomas Gerding, Ph. D.
William Gold, Ph. D.
George S. Goldstein, M.D.
Jack Goodman, Ph. D.
George F. Hoffnagle, Sc. D.

F. Allen Hofmann, D.D.S.
L. Honkomp, M.D.
Dennis Huston
Eugene R. Jolly, M.D., Ph. D.
Joseph L. Kanig, Ph. D.
J. Vernon Knight, M.D.
Gerald Kowitz, D.D.S.
Ralph R. Lobene, D.D.S., M.S.
Jean Lockhart, M.D.
Harold Loe, D.D.S.
Walter J. Loesche, D.M.D., Ph. D.
H. J. Lutz
Irwin Mandel, D.D.S.
John H. Manhold, D.M.D., M.A.
Gerald McCowen
Thomas F. McNamara, Ph. D.
Raymond A. Nelson
James W. Newberne, D.M.D.
M. W. Noall, Ph. D.
Bernard L. Oser, Ph. D.
William J. Phelan, M.D.
Gary Pitts, Ph. D.
Gordon W. Pledger, Ph. D.
Phyllis E. Riley, Ph. D.
Francis J. C. Roe, D.M., F.R.C. Path.
George W. Rogers, M.D.
Norton Ross, D.D.S., M.A.
Eugene R. Rubacky, Ph. D.
Arthur J. Saffir, D.M.D., Ph. D.
Max Samter, M.D.
Irving R. Schmolka, Ph. D.
Gordon Schrotenboer, Ph. D.
H. A. Shelanski, M.D.
Morris V. Shelanski, M.D.
Sigmund S. Socransky, D.D.S.
Robert Stafford
Anthony Volpe, D.D.S., M.S.
Murray Werner, M.D.
C. R. Willis, Ph. D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 14, 1979, in arriving at its conclusions and recommendations.

The charge to the Panel required the review of OTC "oral cavity" drugs. However, the Panel decided to adopt the term "oral health care" when referring to products that are used for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions on the mucous membranes of the mouth and throat. The Panel concluded that "oral health care" would be a more appropriate term to describe the function of these products to the lay public. (See part II. paragraph B.1. below—Introduction, and part II. paragraph B.2. below—Oral health care.) Accordingly, these products are referred to as "oral health care drug products" throughout this document.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC oral health care drug products with respect to the following three categories:

Category I

Conditions under which OTC oral health care drug products are generally recognized as safe and effective and are not misbranded.

Category II

Conditions under which OTC oral health care drug products are not generally recognized as safe and effective or are misbranded.

Category III

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

The Panel reviewed 25 active ingredients for use as oral health care agents. The Panel placed 9 ingredients in Category I, 10 ingredients in Category II, and 3 ingredients in Category III for analgesic/anesthetic use. The Panel placed no ingredients in Category I, 10 ingredients in Category II, and 25 ingredients in Category III as antimicrobials. The Panel placed two ingredients in Category I, one ingredient in Category II, and no ingredients in Category III as astringents. The Panel placed three ingredients in Category I, one ingredient in Category II, and no ingredients in Category III as debriding agents. The Panel placed no ingredients in Category I, no ingredients in Category II, and two ingredients in Category III as decongestants. The Panel placed four ingredients in Category I, no ingredients in Category II, and no ingredients in Category III as demulcents. The Panel placed no ingredients in Category I, one ingredient in Category II, and three ingredients in Category III as expectorants. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of July 20, 1973 (38 FR 19444) requesting the submission of data and information on OTC oral health care drugs, the following firms made submissions relating to the indicated products that, the Panel has further determined, contain active ingredients or labeling which may be appropriately classified as oral health care drug products.

A. Submissions By Firms

Firms and Marketed Products

Ayerst Laboratories, New York, NY 10017; Larylgan throat spray
BASF Wyandotte Corp., Wyandotte, MI 48192; Pluronic polyols
Beecham Products, Parsippany, NJ 07054; Dyclonine hydrocloride lozenges
Blair Laboratories, Inc., Norwalk, CT 06856; Isodine concentrate
Block Drug Co., Inc., Jersey City, NJ 07302; Proxigel
Calgon Consumer Products Co., Inc., Pittsburgh, PA 15236; Sucrets cold decongestant formula lozenges, Sucrets cough control formula lozenges, Sucrets sore throat lozenges
Church and Dwight Co., Inc., Syracuse, NY 13201; Arm and Hammer baking soda
Ciba-Geigy Corp., Summit, NJ 07901; Domiphen bromide
Colgate-Palmolive Co., Piscataway, NJ 08854; Benzethonium chloride mouthrinse
Cooper Laboratories, Inc., Cedar Knolls, NJ 07927; Amosan, oral-B antiseptic drops
Cox Drugs, Biltmore, NC 28803; Formula "U"
Denver Chemical Manufacturing Co., Stamford, CT 06904; Pain-A-Lay
Endo Laboratories, Inc., Garden City, NY 11530; Benzocol, Dyclocol, Lidocol
Glenbrook Laboratories (Division of Sterling Drug, Inc.), New York, NY 10016; Campho-Phenique
Hoyt Laboratories, Needham, MA 02194; Orabase with Benzocaine
Hynson, Westcott and Dunning, Inc., Baltimore, MD 21201; Thantis lozenges
International Pharmaceutical Corp., Warrington, PA 18976; Gly-Oxide liquid
Johnson and Johnson, New Brunswick, NJ 08903; Micrin plus, gargle and rinse
K. I. K. Co., Bethlehem, PA 18016; Cheramist
LaWall and Harrison Research Laboratories, Inc., Philadelphia, PA 19146; Troutman's cough syrup
Lorvic Corp., The, St. Louis, MO 63134; Odara solution
McKesson Laboratories, Fairfield, CT 06430; Isodettes anesthetic throat lozenges
Merrell-National Laboratories, Cincinnati, OH 45215; Cepacol anesthetic troches, Cepacol mouthwash/gargle, Cepacol throat lozenges
Monsanto Industrial Chemicals Co., St. Louis, MO 63166; Methyl salicylate
Norwich-Eaton Pharmaceuticals, Norwich, NY 13815; Chloraseptic aerosol spray, Chloraseptic lozenges, Chloraseptic mouthwash/gargle
Plough, Inc., Memphis, TN 38101; Aspergum
Procter and Gamble Co., The, Cincinnati, OH 45202; Scope mouthwash and gargle
Purdue Frederick Co., The, Norwalk, CT 06856; Betadine mouthwash/gargle
Reed and Carnrick Pharmaceuticals, Kenilworth, NJ 07033; Mouthwash and gargle
Rystan Co., Inc., White Plains, NY, 10605; Chloresium Dental ointment, Chloresium solution, Chloresium tablets
Schmid Laboratories, Inc., Little Falls, NJ 07424; Potassium chlorate, Ferric chloride, Balsam tolu, Glycerite of boroglycerin
Scott Laboratories, Inc., Corpus Christi, TX 78408; Scott's certified peroxide of hydrogen
Squibb Pharmaceutical Co., Princeton, NJ 08540; Spect-T decongestant lozenges, Spect-T cough suppressant lozenges, Spect-T anesthetic lozenges, Spect-T sore throat spray

Sterling Drug, Inc., New York, NY 10016; Campho-Phenique liquid, Campho-Phenique powder
Thayer, Henry, Co., Cambridge, MA 02138; Thayer slippery elm throat lozenges
Upjohn Co., The, Kalamazoo, MI 49001; Oral pentacresol
Vick Chemical Co., New York, NY 10017; Vicks medi-trating throat lozenges, Vicks oracin throat lozenges
Warner-Lambert Co., Morris Plains, NJ 07950; Listerine antiseptic, Listerine throat lozenges
Warren-Teed Pharmaceuticals, Inc., Columbus, OH 43215; Di-O-Chrome
Whitehall Laboratories, Inc., New York 10017; Anbesol

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Acetanilid
Alcohol
Alum
Ammonium chloride
Anise oil
Antipyrine
Aromatics
Aspirin
Benzethonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
Borax
Boric acid
Boroglycerin
Calcium chloride
Calcium silicate
Camphor
Caramel
Carbamide peroxide
Carbolic acid
Cetyldimethylbenzylammonium chloride
Cetylpyridinium chloride
Chloroform
Chlorophyll "A" water-soluble derivatives
Cinnamon oil
Cresol
Dextromethorphan hydrobromide
Dextrose
Dibucaine hydrochloride
Domiphen bromide
Dyclonine hydrochloride
Elm bark
Essential oils
Eucalyptol
Eucalyptus oil
Ferric chloride
Gelatin
Gentian violet
Glycerin
Glycerol, anhydrous
Hexylresorcinol
Honey
Horehound
Hydrogen peroxide
Iodine
Isobornyl acetate
Lidocaine
Lidocaine hydrochloride
Menthol
Merodicein
Methylparaben
Methyl salicylate
Pectin
Peppermint oil
Phenol
Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride
Phosphate buffers
Plasticized hydrocarbon gel (polyethylene in mineral oil)
Potassium chlorate
Potassium chloride
Potassium iodide
Povidone-iodine
Povidone-iodine, concentrate
Propylene glycol
Propylparaben
Pyrilamine maleate
Sage oil
Saligenin
Secondary-amyltricresols
Sodium bicarbonate
Sodium bitartrate buffer
Sodium borate
Sodium caprylate
Sodium carboxymethylcellulose
Sodium chloride
Sodium dichromate
Sodium perborate
Sodium peroxyborate monohydrate
Sodium phenolate
Sodium saccharin
Sorbitol base
Spearmint oil
Sugar
Talcum power
Thymol
Tincture of myrrh
Tolu balsam
Urea peroxide
Vegetable stearate
Water
Wintergreen oil
Zinc chloride

2. *Other ingredients reviewed by the Panel.*

Benzalkonium chloride
Dequalinium chloride
Dibucaine
Nitromersol
Oxyquinoline sulfate (8-hydroxyquinoline)
Tetracaine
Tetracaine hydrochloride
Thymol iodide

C. Classification of Ingredients.

1. *Active ingredients.*

Anesthetics/Analgesics

Antipyrine
Aspirin
Benzocaine
Benzyl alcohol
Camphor
Cresol
Dibucaine
Dibucaine hydrochloride
Dyclonine hydrochloride
Eucalyptol (eucalyptus oil)
Hexylresorcinol
Lidocaine
Lidocaine hydrochoride
Menthol
Methyl salicylate (wintergreen oil)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Pyrilamine maleate
Salicyl alcohol (saligenin)
Tetracaine
Tetracaine hydrochloride
Thymol

Antimicrobial Agents

Benzalkonium chloride
Benzethonium chloride
Benzoic acid
Boric acid
Boroglycerin glycerite (boroglycerin)
Camphor
Carbamide peroxide in anhydrous glycerin (carbamide peroxide, urea peroxide)
Cetalkonium chloride (cetyldimethylbenzylammonium chloride)
Cetylpyridinium chloride
Chlorophyll (chlorophyll "A" water-soluble derivatives)
Cresol
Dequalinium chloride
Domiphen bromide
Ethyl alcohol (alcohol)
Eucalyptol (eucalyptus oil)
Ferric chloride
Gentian violet
Hydrogen peroxide
Iodine
Menthol
Meralein sodium (merodicein)
Methyl salicylate (wintergreen oil)
Nitromersol
Oxyquinoline sulfate (8-hydroxyquinoline)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Potassium chlorate
Povidone-iodine (povidone-iodine, concentrate)
Secondary amyltricresols (secondary-amyltricresols)
Sodium caprylate
Sodium dichromate
Thymol
Thymol iodide
Tincture of myrrh
Tolu balsam

Astringents

Alum
Tincture of myrrh
Zinc chloride

Debriding Agents

Carbamide peroxide in anhydrous glycerin (carbamide peroxide, urea peroxide)
Hydrogen peroxide
Sodium bicarbonate
Sodium perborate (sodium peroxyborate monohydrate

Decongestants

Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride

Demulcents

Elm bark
Gelatin
Glycerin
Pectin

Expectorants

Ammonium chloride
Horehound
Potassium iodide
Tolu balsam

2. *Inactive ingredients.* The Panel has classified the following as inactive ingredients or pharmaceutical necessities. The list is not intended to be exhaustive.

Acetanilid
Anise oil
Aromatics
Calcium chloride
Calcium silicate
Caramel
Cinnamon oil
Dextrose
Essential oils
Glycerol, anhydrous
Honey
Isobornyl acetate
Methylparaben
Peppermint oil
Phosphate buffers
Plasticized hydrocarbon gel (polyethylene in mineral oil)
Potassium chloride
Propylene glycol
Propylparaben
Sage oil
Sodium bitartrate buffer
Sodium borate (borax)
Sodium carboxymethylcellulose
Sodium chloride
Sodium saccharin
Sorbitol base
Spearmint oil
Sugar
Talcum power
Vegetable stearate
Water

3. *Ingredient previously reviewed by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in the* **Federal Register** *of September 9, 1976 (41 FR 38312).* Dextromethorphan hydrobromide.

4. *Ingredient removed from all drug products.* On June 29, 1976, a notice was published in the **Federal Register** (41 FR 26845) which prohibited the use of chloroform as an ingredient (active or inactive) in drug products. Studies conducted by the National Cancer Institute demonstrated that oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Section 310.513 (21 CFR 310.513) was established to remove chloroform from all drug products.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in reponse to the call-for-data notice published in the **Federal Register** of July 20, 1973 (38 FR 19444). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 24, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions

The following are definitions of terms used in this document.

1. *Antimicrobial agent.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to claimed effects of the product in which it is included.

2. *Antimicrobial preservative.* A compound or substance that kills organisms or prevents or inhibits their growth and reproduction and is included in a product formulation only at a concentration sufficient to prevent spoilage or prevent growth of inadvertently added microorganisms, but does not contribute to the claimed effects of the product to which it is added.

3. *Astrigent.* An agent that causes contraction of the tissues or arrest of secretions by coagulation of proteins on a cell surface.

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

5. *Decongestant.* An agent that reduces congestion or swelling. In OTC use for mucous membranes the term generally refers to adrenergic drugs that act by vasoconstriction.

6. *Debriding agent.* An agent which causes the removal of foreign material or devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion to expose surrounding healthy tissue.

7. *Demulcent.* A bland, inert agent that soothes and relieves irritation of inflammed or abraded surfaces such as mucous membranes.

8. *Expectorant.* An agent that promotes the expectoration (spitting) of mucus or of respiratory tract secretions by decreasing the viscosity.

9. *Gargle.* A fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat.

10. *Germicide.* An agent that destroys microorganisms. The term includes bactericide, fungicide, virucide, and amebicide.

11. *Hydrophilic.* A substance which has a marked affinity for water.

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

13. *In vivo study.* A study performed in living animals or people.

14. *Iodophor.* There are at least three categories of iodophors: (1) Hydroalcoholic solutions of elemental iodine and iodides, (2) elemental iodine complexed with various surfactant compounds, and (3) elemental iodine complexed with various nonsurfactant compounds such as PVP-iodine complex (povidone-iodine).

15. *Lipophilic.* A substance with a pronounced affinity for fats (lipids).

16. *Mouth odor.* A general term for an odor emanating from the oral cavity. It may or may not be offensive. When such odor is perceived as unpleasant, obnoxious, offensive, or objectionable, a term such as "malador," "halitosis," or "bad breath" is used.

17. *Mouthwash.* A solution used for rinsing the mouth, not necessarily for medicinal purposes.

18. *Oleoresin.* A natural combination of a volatile oil and a resin, such as exudes from pines and other plants.

19. *Oral cavity.* The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands whose ducts open into it, the teeth, and the tongue. For purposes of this Panel, the teeth and gums are excluded since they were considered by the Advisory Review Panel on OTC Dentifrices and Dental Care Drug Products.

20. *Oral health care.* The proper care of the mouth, including the temporary relief of symptoms of the mouth and throat, for example, occasional minor sore throat or mouth soreness.

21. *Organoleptic.* A property of a substance which makes an impression upon one or more of the organs of special sense (such as taste or smell), thereby affecting the flavor, odor, or appearance of a drug product.

22. *Pharynx (throat).* The musculomembranous sac between the mouth and nostrils and the esophagus. It is continuous below with the esophagus and above communicates with the mouth, nasal passages, and auditory (Eustachian) tubes. It is subdivided into the following parts:

(a) *Nasopharynx.* The part above the level of the soft palate.

(b) *Oropharynx.* The part that lies between the soft palate and the upper edge of the epiglottis.

(c) *Laryngopharynx.* This lies between the upper edge of the epiglottis and opens into the larynx and esophagus (sometimes called hypopharynx).

23. *Sialagogue.* An agent which promotes the flow of saliva.

24. *Topical analgesic.* A substance applied to an epithelial surface (e.g., skin or mucous membrane) that relieves pain without necessarily abolishing other sensations; or one that causes partial blockade of subcutaneous or submucosal terminal nerve endings so that a minimal stimulus evokes no painful response, but a greater stimulus does. In this document the term anesthetic has been adopted to conform with established ursage. Adoption of the term "anesthetic" does not preclude the use of the term "analgesic" when appropriate or preferable.

25. *Topical anesthetic.* A substance applied that completely blocks pain receptors resulting in a sensation of numbness and abolition of responses to painful stimuli.

B. General Discussion

1. *Introduction.* The Panel was convened and charged to evaluate ingredients in OTC preparations used for oral health care. These ingredients are intended to be used for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions on the mucous membrances of the oral cavity (mouth) and pharynx (throat). Ingredients intended for the relef of symptoms airising from the teenth and gums were not evaluated by the Panel because ingredients for such use were reviewed by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. The Oral Cavity Panel has reviewed these ingredients and evaluated them strictly from the standpoint of the symptomatic relief that they are intended to promote. The ingredients evaluated are applied directly to the mucous membranes of the mouth and throat and act locally. They are not intended to be curative, nor are they intended to be used by consumers in the self-diagnosis and treatment of afflications of the mouth and throat. Ingredients known or presumed to be absorbed and to act systemically were either deferred to other Panels for evaluation or classified as Category II. The Panel emphasizes that the ingredients evaluated by the Panel relieve symptoms that are self-limiting and that these ingredients are not for use as curative agents.

The Panel was charged to evaluate individual ingredients for safety and effectiveness for indications claimed in the labeling of OTC products in light of present-day knowledge and standards used in pharmacology, therapeutics, and toxicology. In making its evaluation, the Panel relied heavily upon factual data found in standard textbooks and scientific articles published by independent investigators in medical, dental, and other scientific journals. Some of these articles were incorporated by manufacturers into their submissions to the FDA to provide a scientific basis for claims made for the safety and effectivness of their ingredients. Data supplied by manufacturers in unpublished reports of studies performed by private laboratories under contract to the manufacturers or in manufacturers' laboratories were also used by the Panel in making judgments. The Panel also gave due consideration to data from marketing experience and widespread clincial usage. The Panel regards such data as corroborative when in agreement with basic data from controlled studies and scientific facts. The Panel placed little reliance upon such data, however, when insufficient pharmacologic, therapeutic, and toxicity studies were supplied. The Panel felt it was under no obligation to make a judgment on the safety and effectiveness of ingredients relying solely on marketing data supplied by the manufacturers in their submissions.

The Panel has considered the ingredients in the submissions and has grouped them according to their pharmacologic activity and modes of action. It has deferred to other Panels for consideration, or classified as Category II, those ingredients believed to exert their claimed effects systemically after absorption from the mucous membrances of the oral cavity or those ingredients that have no effect on the mucous membrances.

In its review of ingredients of oral health care products, the Panel has identified two groups having a general similarity based on indications for recommended use. The first group, consisting principally of mouthwashes, rinses, or sprays, is offered for cleansing of the mouth, elimination of mouth odors, and other hygienic or cosmetic purposes. In most cases products in this group are recommended for use on a continuing basis in situations in which no symptoms or evidence of disease are present. Many are recommended for use on a day-to-day basis with no specified limits on time or quantities of usage. Some are recommended for prophylaxis for oral cavity diseases.

The products in the second group are offered for short-term therapy to relieve symptoms of sore throat and sore mouth. Definite evidence of a pathologic process exists, and a limit has been placed on the time the product is recommended for use. In some cases, overlapping exists and the indications of the first group also encompass some of the indications for products in the second group. The Panel has evaluated the ingredients in each of the products in these groups on the basis of therapeutic effectiveness in relieving symptoms of pathologic processes given rise to sore mouth or sore throat or both. Claims made for ingredients in oral health care products that do not meet these criteria, i.e., relief of symptoms, are considered to be Category II claims.

Some products list active ingredients for which no claim for indications for use are made in the labeling. Products containing such ingredients are considered to be misbranded.

The Panel has identified the major pharmacologic groups as listed below from the claims made for the active ingredients in the labeling of OTC products. The active ingredients are discussed in statements, elsewhere in this document, according to this pharmacologic classification. Certain drugs have more than one action and have more than one therapeutic claim made for such actions. Therefore, such ingredients appear under two or more different pharmacolgic classes in the ingredient discussions below. Phenol, for example, is claimed to exert both a topical anesthetic effect and an antimicrobial effect. The Panel has considered the chemistry, pharmacology, toxicology, safety, and effectiveness of phenol in the discussions of this ingredient. Its safety and effectiveness are discussed first as an anesthetic in the section on anesthetics/analgesics. (See part III. paragraph b.l.g. below—Phenol.) The effectiveness of phenol as an antimicrobial agent is then described in the section on antimicrobial agents. (See part IV. paragraph B.3.r. below—Phenol.)

The Panel has identified the following pharmacologic groups of ingredients and described each one, their modes of action, and their effects, elsewhere in this document:

a. Anesthetics/Analgesics.
b. Antimicrobial agents.
c. Astringents.
d. Debriding agents.
e. Decongestants.
f. Demulcents.
g. Expectrorants.

Anesthetics may also be recognized as analygesics. It is well known and accepted that anesthetics, in low concentrations, may and will usually act as analgesics. However, not all

analgesics exert an anesthetic effect at higher doses. The Panel has adopted the term "anesthetic/analgesic" in this document for the purpose of grouping these ingredients for ease of review. Adoption of this term does not preclude the use of the terms "anesthetic" or "analgesic" in labeling, as appropriate, and the Panel leaves the choice of selecting either of these terms to the manufacturer. The Panel, however, concludes that it is not acceptable to use the term "anesthetic" in the labeling of a product which contains an analgesic, i.e. aspirin, as its only active ingredient.

An ingredient having more than one pharmacologic action, as for example phenol, may be classified in one category (Category I) as an anesthetic and in another category (Category III) as an antimicrobial agent. Other ingredients in more than one pharmacologic group for use on the mucous membranes of the mouth and throat have similarly been evaluated by the Panel for their safety and effectiveness.

The mouth and throat are continuous with the lower respiratory and gastrointestinal tract. There are many ingredients that may act on the mucous membranes of these structures. However, these ingredients are considered primarily from the standpoint of the effect that they exert on the mucous membranes of the mouth and throat.

In some cases, the action of certain drugs may be selective and exert a greater effect in some tissues than in others. In other cases, the responses of drugs and their differences are merely quantitiative and relative, and depend upon the number of cells or receptors on the cells being affected. Various degrees of predilection for certain cells may occur with changes in conditions, or dosage, or pH, etc. The mechanism and selective action of the drug may depend upon differences of penetration or upon chemical affinity of the drug for the cells or the changes in the sensitivities to the action of the drug. The drug may also act on the cell without actually penetrating into it, as for example, by exciting or depressing the nerve supplying the cell. A drug may act directly on the cell surface and alter its function by withdrawing water from the cytoplasm. As a general rule, the drug must pass into the cell or cell membrane before it can exert any action, and, in order for absorption to occur, the drug must be soluble in the constituents of the cell membrane. The solubility of a drug in the cell membrane and cytoplasm is not necessarily the same as it is in water. It may vary for each kind of cell, and consequently the penetration of drugs into the different cells may vary (Refs. 1, 2, and 3).

In some cases, a concentration of a sustance that accumulates in a cell may be greater than that present in the external environment. This concept holds true expecially if the substance undergoes selective concentration. This may be due to the fact that the ingredient binds with proteins and cell constitutents and attains a concentration that is pharmaceutically active. Some of the aforementioned principles apply to absorption from the mucous membranes of the mouth and throat and are described in more detail below.

References

(1) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 17–31, 1965.

(2) Fingl, E., and D. M. Woodbury, "General Principles," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 16–25, 1970.

(3) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 21–30, 1976.

2. *Oral health care.* The Panel has adopted the term "oral health care" in referring to the use of products intended for the relief of symptoms due to pathologic states in the mouth and throat and refers to these products as oral health care products. The Panel is aware of the widespread use of the term "oral hygiene" and the fact that it is in some cases used to support therapeutic claims for pathologic states in the mouth in the labeling of some oral cavity products. Consumers associate the term with cleansing agents and other cosmetic products for use in the mouth on a daily basis or more often. The Panel feels that the term "oral hygiene" should be reserved exclusively for use in the labeling of cosmetic products used for cleaning and similar purposes to maintain a healthy state of the mouth and not for identifying a product as one having therapeutic claims. The Panel, therefore, considers labeling such as "for oral hygiene" a Category II claim if a product having such labeling is intended to be used for therapeutic purposes.

The mouth and nose are the portal of entry of a variety of microorganisms (Ref. 1). These may remain in the mouth, nasopharynx, and throat, or they may remain in the gastrointestinal tract or respiratory system. Normally they do not cause disease. The oral cavity is endowed with physiologic mechanisms for maintianing a healthy state of the structures contained therein. In essence, no medications are needed to achieve this end. The secretions of the salivary, mucous, and serous glands lubricate and maintain a healthy state of the mucous membrances and other structures in the mouth. The indigenous flora of the oral cavity consits of nonpathogenic microorganisms which seldom produce disease. They help maintain a balance of the microbial population and probably play an important role in maintianing a healthy state of the oral cavity.

Normally, approximately 0.25 to 1.0 milliliter (mL) of saliva is excreted per minute or about 1,500 mL per 24 hours. This, together with the secretions of the mucous glands, acts as a diluent, has a cleansing action, and moistens the mucous membrances. It cleans the mouth and teeth and may inhibit bacterial growth. The flow of saliva can be modified by various normal stimuli (Refs. 2, 3, and 4).

In addition to the above-mentioned protective mechanism, immunologic defense mechanisms, particularly those involving the action of immunoglobulin A (IgA), are also present. These interfere with adherence of microogranisms to mucosal surfaces by causing them to aggregate, rendering them susceptible to phagocytosis (Refs. 1, 5, and 6).

In fever and during certain illnesses, the flow of saliva and secretion of mucus may be decreased. Orgnic material may accumulate and decompose, and bacterial growth is no longer inhibited. A foul odor may develop, and ulcerations and inflammation of the mucous membrances may result (Ref. 2). Sore mouth, discomfort, or pain may also develop, making treatment desirable. Since a pathologic state exists in such situations, claims may be made for the use of OTC oral health care products to relieve these symptoms. However, the labeling should clearly indicate that if the symptoms persist, professional advice should be sought. It is the consensus of the Panel that claims implying that an OTC product can be used for oral health care and can prevent the development of such a pathologic state in a person who is not in good health are not acceptable. Claims that state or imply that the prophylactic use of an OTC oral health care product maintains a healthy state are misleading to a consumer.

References

(1) Greenpan, J. S., and R. J. Boackle, "Oral and Dental Diseases," *in* "Basic and Clinical Immunology," 2d Ed., edited by H. H.

Fudenberg et al., Lange Medical Publications, Los Altos, CA, pp. 673–676, 1978.

(2) Hightower, N. C., "Salivary Secretions," *in* "The Physiological Basis of Medical Practice: A Text in Applied Physiology," 8th Ed., edited by C. H. Best and N. B. Taylor, Williams and Wilkins Co., Baltimore, pp. 1076–1080, 1966.

(3) Best, C. H., and N. B. Taylor, "The Human Body: Its Anatomy and Physiology," 4th Ed., Holt, Rinehart, and Winston, New York, pp. 294–301, 1963.

(4) Gates G. A., "Physiology of the Salivary Glands," *in* "Otolaryngology: Volume 1, Basic Sciences and Realted Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 347–356, 1973.

(5) Hong, R., "Basic Principles of Immunology," *in* "Otolaryngology: Volume 1, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 715–725, 1973.

(6) Hauptman, S. P., and T. B. Tomasi, "The Secretory Immune System," *in* "Basic and Clinical Immunology," 2d Ed., edited by H. H. Fudenberg et al., Lange Medical Publications, Los Altos, CA, pp. 205–216, 1978.

3. *The anatomy and physiology of the oral cavity.* The oral cavity extends from the lips to the anterior pillars of the fauces and is lined by the oral mucous membrane. The mucous membrane is composed of connective tissue covered by stratified squamous epithelium. Modifications of this basic pattern occur in different areas of the mouth and are related to differing functions. The hard palate, gingiva, and the tips of the papillae on the dorsum of the tongue are the only areas where keratinization normally occurs in the oral cavity of human beings.

a. *The oral mucous membrane.* The oral cavity is concerned with proprioception, taste, and mastication (chewing) of food. During the process of mastication, the food is mixed with saliva and the enzymes in the saliva initiate digestion. Stern (Ref. 1) divides the oral mucosa into three major types: (1) Masticatory mucosa (gingiva, hard palate); (2) lining or reflecting mucosa (lip, cheek, vestibular fornix, alveolar mucosa, floor of mouth, and soft palate); and (3) specialized mucosa (dorsum of the tongue and taste buds).

The masticatory mucosa is bound to bone and does not stretch. The lining mucosa covers the musculature and is distensible. It covers all the surfaces of the mouth except the dorsum of the tongue and the masticatory mucosa. The specialized (sensory) mucosa bears the taste buds, which have a sensory function.

The oral mucous membrane is composed of two layers, epithelium and connective tissue (lamina propria). The dermal papillae contain blood vessels and nerves and interdigitate with the epithelial ridges. At the junction of the two tissues are the basal lamina and the basement membrane. The basal lamina is not ordinarily discernible with the light microscope, but is evident at the electron misroscopic level and is epithelial in origin. The basement membrane is evident at the light microscopic level. It is a relatively cell-free zone that is 1 to 4 microns thick and found within the connective tissue, subjacent to the basal cells. This zone stains positively with the periodic acid-Schiff method, indicating that it contains neutral mucopolysaccharides (glycosaminoglycans). It also contains fine argyophilic silver staining reticular fibers, as well as special anchoring fibrils.

The lamina propria may be attached to the periosteum of the alveolar bone, or it may overlay the submucosa, which varies in thickness in different regions of the oral cavity, such as the floor of the mouth and the soft palate.

The submucosa attaches the mucous membrane to the underlying structures. Within this layer are glands, blood vessels, nerves, and adipose tissue. The sensory nerves to the mucous membrane tend to be more concentrated at the anterior part of the mouth. The nerve fibers are myelinated in the submucosa, but lose their myelin sheaths before splitting into their end arborizations. Sensory nerve endings of various types are found in the papillae. Some of the fibers enter the epithelium, where they terminate between the epithelial cells as free nerve endings. The blood vessels are accompanied by nonmyelinated visceral nerve fibers that supply their smooth muscle. In those areas of the mouth where the submucosa is lose, the mucous membrane is movable over the deeper layer. On the other hand, where the submucosa is dense the mucous membrane does not move over the deeper structures.

The epithelium of the oral mucosa is stratified squamous. It may be keratinized, parakeratinized, or nonkeratinized depending on location. In the oral cavity of humans, only the gingiva and the hard palate are normally keratinized, although in many individuals the gingival epithelium is parakeratinized. The cheek, faucial, and sublingual tissues are normally nonkeratinized.

The four cell layers which are found in keratinizing oral epithelium are the basal, spinous, granular, and cornified layers. The basal cell which ultimnately forms keratin at the surface is called the keratinocyte.

Reference

(1) Stern, I. B., "Oral Mucous Membrane", *in* "Orban's Oral Histology and Embryology," 8th Ed., edited by S. N. Bhaskar, C. V. Mosby Co., St. Louis, pp. 253–327, 1976.

b. *The physiology of pain.* Pain is difficult to define. There is little point in attempting to formulate a definition of a subjective sensation that is clearly known to each individual by experience and the nature of which is described by illustration. Pain is the most common symptom for which people seek relief. It is an experience that embodies both the capacity to be discriminative and the ability to interpret the nature of a stimulus by reference to present and past experiences (Ref. 1).

Obviously, it is best to determine the etiology of a pain and treat the causative factor, be it a disease process, the result of trauma, or a functional disturbance. Nonetheless, self-limited, mild to moderate pain in the mouth and throat may be treated symptomatically by self-medication.

Sensory receptors are present in the mucous membranes, the submucosal tissues, and the muscular and other structures of the oral cavity for the perception of pain, cold, warmth, touch, pressure, proprioception, and taste (Refs. 2 and 3). A discussion of receptors for pain, cold, warmth, touch, and pressure follows because they are stimulated by certain ingredients used in oral health care products such as camphor, menthol, etc. Furthermore, if subjected to greater-than-ordinary stimulation they may be sensed as pain. Receptors for taste are located in the tongue and are discussed below along with the receptors for smell, which are located in the nose. The receptors for taste and smell act in consort, since what a person interprets as taste may actually be due to smell. Since many drug preparations used in the oral cavity contain distasteful ingredients and flavors, odoriferous ingredients are added to assure patient acceptance. Therefore, the sensations of taste and smell assume importance in OTC oral health care products and are discussed below. (See part II. paragraph B.3.c. below—The physiology of taste. See also part II. paragraph B.3.d. below—The physiology of smell.)

Topical anesthetics act at the site of application of a drug after they penetrate the mucous membranes and come into contact with these sensory receptors. These receptors are connected to terminal fibers of networks of nerves that are present in the various layers of the epithelial membrane and other tissues.

Each type of receptor ordinarily perceives its own type of sensation. They can also respond to thermal, mechanical, chemical, or painful stimuli and induce the sensation of pain. Stimuli of greater intensity than normally required to activate them may produce the sensation of pain. Sensory receptors are classified as follows: (1) *Receptors for pain.* These consist of "bare" nerve endings that receive the stimuli incited by pain directly and transmit them along larger nerve trunks to the central receptors in the brain. Itching is not ordinarily perceived in the oral cavity; yet it has been perceived on rare occasions, particularly in areas covered by stratified squamous epithelium or at the mucocutaneous junctions. The sensation of itch is carried along the same receptors as that of pain. The principal difference is that the intensity of the stimulus or the frequency of impulses for inducing itch are less than the impulses for inducing pain (Refs. 3 and 4). The nerve fibers carrying the sensation of pain and itch are mostly of the small unmyelinated C type sensory nerve fibers (Ref. 1). Some delta A myelinated fibers may also play a role. Pain fibers are not uniformly distributed over the mucous surfaces. They are more concentrated on the tongue, in the pharynx, along the lips, and less so in areas such as the palate and floor of the mouth. The activity of these receptors is obtunded partially or completely by topical analgesics and anesthetics. The modes of action of analgesics and anesthetics are described below. (See part III. paragraph A.1. below—Modes of action.) The pain receptors appear to be affected more easily and readily than the receptors for other sensations listed above probably because they are small and unmyelinated nerve fibers and are thereby easily penetrated by drugs (Ref. 3).

(2) *Receptors for cold.* The end bulbs of Krause are oval sense organs that perceive the sensation of cold. These nerve endings may be blocked simultaneously with the pain receptors by topical anesthetics. Whether or not they are blocked depends upon the concentration of anesthetic that reaches them and the degree of penetration. They may be stimulated by some ingredients, such as menthol or camphor, and produce a sensation of coolness that masks the sensation of pain. Some counterirritants may act by stimulating these receptors. Counterirritants and rubefacients, however, have no place as therapeutic agents in OTC oral health care products.

(3) *Receptors for warmth.* The end organs of Ruffini are cylindrical end organs in the mucous membranes that perceive the sensation of warmth. They may also be partially or completely blocked simultaneously by anesthetic ingredients, depending upon the concentration and the duration of contact of the ingredient. These receptors are stimulated by some ingredients, such as camphor and alcohol, by some flavorants, and by some rubefacients, such as methyl salicylate, which are all present in OTC oral health care products.

(4) *Receptors for pressure.* Pacinian Corpuscles are cylindrical end organs in the skin that perceive the sensation of deep pressure. Anesthetics in concentrations exceeding those needed to block pain receptors may be needed to block these receptors.

(5) *Receptors for touch.* Meissner's corpuscles are end organs in the mucous membranes that perceive the sensation of touch and respond to tactile stimuli. They may also be partially or completely blocked by anesthetics (Refs. 2 and 3). They may be stimulated by the presence of exudates, mucous, and other secretions that collect on mucous membranes.

Pain on epithelial surfaces is well-defined and easily localized. Pain arising in structures beneath the mucous membranes may be poorly localized and is usually dull in character. It may, however, be sharp in some cases and spread or radiate in a distinct pattern. Pain is frequently "referred," i.e., felt at locations remote from its source (Refs. 3 and 4). It is not uncommon to experience deep-seated pain in structures in the oral cavity or the pharynx, Pain arising from a localized aphthous ulcer beneath the tongue, for example, may radiate along the entire lower jaw to the tongue, into the nose or even the head. Pain in the pharynx may radiate to the ear via the anterior or posterior pillars to the Eustachian tube. The oral cavity is richly supplied with sensory receptors from filaments of the fifth cranial nerve. Most structures in the mouth are extremely sensitive to painful as well as other stimuli. In addition, the ninth cranial (glossopharyngeal) nerve as well as filaments of the tenth cranial (vagus) nerve also provide a sensory supply to the posterior portion of the tongue, and oro-and hypopharynx, The ability to identify and localize pain is not inborn; it is learned from past experience.

Pain originating from bones, joints, and tendons may induce muscle spasm and cause pain in the affected muscles. Induced spasm or chronic muscle injury, with pain, is a part of an involuntry defensive mechanism whereby the patient attempts reflexively to immobilize a painful joint (Ref. 5). This is not uncommon in the oral cavity when spasm of the muscles of mastication attempt to immobilize the temporomandibular joint. The muscles of the pharyngeal wall may also go into spasm when swallowing occurs in cases of sore throat.

Relief of pain involves two components: raising the pain threshold and altering the psychologic response to pain. The pain threshold varies little from one individual to the next, but the psychological response to pain varies greatly among individuals and in the same individual under different circumstances and in different settings. What may be referred to as a slight pain by one individual may be interpreted as a severe pain by another. Time, place, environmental and social factors, cultural background and family response patterns, emotional status, age, and past experiences may all influence an individual's response to pain and interpretation of the "meaning" of the stimulus. Anxiety is an important factor in the interpretation of pain. The number of individuals who experience pain in which there is no anxiety component is few, indeed (Refs. 1, 3, and 4).

The placebo effect is an important factor to be considered in the evaluation of pain, not only in OTC self-medication, but in all aspects of the healing arts. The psychosomatic contribution of the placebo effect in the evaluation of pain and drugs that relieve pain is a mandatory consideration in any well-designed and meaningful study. The response of an individual's pain perception to a placebo effect is independent of the cause of the pain or of the mechanism inducing the pain. It is more likely that it is discernible if pain is intense. The placebo effect is not peculiar to "neurotic" individuals, and it is not predictable (Refs. 1 and 6).

The intensity of a pain is not necessarily dependent on the severity of the lesion or the pathologic process causing it. A small aphthous ulcer beneath the tongue at the frenulum may cause marked discomfort and cause the pain to radiate into the tongue and lower jaw. On the other hand, a large circumscribed lesion on the hard palate may cause little or no discomfort. Many mouth and pharyngeal (throat) lesions cause little or no discomfort while the patient is quiet, does not talk or attempt to chew or swallow. Any of these activities may incite the pain. Discomfort may result when acidic liquids are ingested and come into contact with the lesions. On the other hand, such lesions of the mouth and throat are little affected or stimulated by

bland substances. Discomfort may also be felt when lesions are covered by exudates. Such discomfort may be relieved by removal of the exudates by using rinses, debriding agents, and in some cases astringents, or by the application of demulcents. The pain ususally recurrs when the exudate reappears.

The Panel concludes that OTC anesthetic/analgesic ingredients are useful for the treatment of the symptoms of occasional minor throat and mouth pain. A pain is usually described as either mild to moderate or severe. Moderate pain may be self-limited and require no special treatment or prior diagnosis by a physician. It is usually relieved by OTC drugs. In some cases, mild pain is referred to as a "minor irritation." Diagnosis and treatment by a physician may not be required for occasional minor irritations and minor pains. Anesthetics, therefore, are often desirable to reduce their intensity and provide relief and comfort. Individuals who must maintain normal daily activities often find these agents useful in providing comfort. The Panel emphasizes that none of the ingredients used in the oral cavity to relieve pain are curative.

The Panel concludes that the most appropriate indication for the relief of pain by OTC anesthetic/analgesic agents should state "for the temporary relief of occasional minor irritation, pain, sore throat, and sore mouth." The Panel recommends the use of the term "occasional" because recurrent or chronic pain, even though of minor intensity, may require diagnosis by a physician to determine the cause.

References

(1) Kabler, J. F., "Neural Mechanisms of Pain," Independent Study Program, Unviersity of Wisconsin Medical School, pp. 6–14, September 1975, draft of unpublished paper in OTC Volume 06B189.

(2) Best, C. H., and N. B. Taylor, "The Physiological Basis of Medical Practice: A Text in Applied Physiology," 7th Ed., Williams and Wilkins Co., Baltimore, pp. 1139–1149, 1961.

(3) Kolodny, A. L., and P. T. McLoughlin, "Comprehensive Approach to Theory of Pain," Charles C. Thomas Publisher, Springfield, IL, pp. 3–30, 1966.

(4) Wolff, H. G., and J. D. Hardy, "On the Nature of Pain," *Physiological Reviews,* 27:167–199, 1947.

(5) Kabler, J. F., "Muscle Pain," Independent Study Program, University of Wisconsin Medical School, pp. 15–28, April 1973, draft of unpublished paper in OTC Volume 06B189.

(6) Beecher, H. K., "The Powerful Placebo," *Journal of the American Medical Association,* 159:1602–1606, 1955.

c. *The physiology of taste.* Smell and taste are interrelated chemical senses. Their importance in patient acceptance of a product used in the oral cavity has been mentioned above. The receptors for taste are chemoreceptors which respond to chemical stimuli. A substance must first be dissolved to arouse a sensation of taste. It may be taken either in solution or dissolved in the saliva or mixed with moistened food or other ingredients. A solid that is placed in a perfectly dry mouth generally cannot be tasted (Refs. 1 through 4).

The anterior two-thirds of the upper surface (dorsum) of the tongue has numerous minute projections of the mucous membrane called papillae. The papillae at the edges, the tip, and the most anterior portion of the dorsum of the tongue are small, conical, cylindrical, or mushroom-shaped structures. They impart a velvety character to this part of the mucosa of the tongue. They are referred to as being filiform (threadlike) or fungiform (mushroomlike) in character, depending on their shape. The most posterior part of the tongue surface is rougher than the anterior due to the presence of papillae that are considerably larger than papillae on the anterior part of the tongue surface. These are peculiar in construction since each is surrounded by a groove or trench. The whole structure has been described as resembling a squat tower surrounded by a moat. They are, therefore, called "vallate papillae", after the Latin word "vallatus" meaning walled (Refs. 1 through 4).

Imbedded in the covering of both large or small types of papillae are groups of slender cells with hairlike processes that are packed lengthwise in bundles. The cells are the receptors of taste. The bundles are called tastebuds. Each cell receives a filament from one of the nerves of taste. The tastebuds open upon the surface of the papillae through a small pore. The ends of the cell converge toward this point where their processes become massed together. Substances in solution enter the pores and act as chemical stimuli. A few scattered tastebuds are present on the extreme posterior (pharyngeal) portion of the tongue and even in the mucosa of the epiglottis.

Four fundamental sensations of taste have been delineated: Sweet, bitter, sour, and salty. Two others are sometimes mentioned, alkaline and metallic. The various other types of tastes that are described are due to a blending of some or all of the fundamental sensations or to a combination of the latter with sensations caused by stimulation of ordinary sensory receptors of pain in the mouth that have been described above. (See part II. paragraph B.3.b. above—The physiology of pain.) Ginger, for example, is not recognized by its actual taste, that is, by stimulation of tastebuds, but by the burning sensation that results from excitation of the other sensory receptors in the mouth, such as those for warmth. Oils are unpleasant to taste, especially because of their consistency which causes a peculiar feeling due to stimulation of the receptors for touch. Acetic and other acids have a sour taste, but also give rise to a burning sensation since they act on other sensory receptors. This is confused in interpretation in the mind with the sense of taste and blended with it (Refs. 1 through 4).

Many of the finer flavors interpreted as tastes are in reality sensations of smell. Smell enters largely into the many sensations attributed to taste. For this reason, when the nose is held or the nasal mucous membrane is inflamed and the nasal passages are occluded, as by an ordinary cold, the sense of taste is blunted.

On the other hand, certain substances which are thought to be detected by smell are actually recognized by the sense of taste. Chloroform is an example of such a substance. The sweetish smell of chloroform is sensed when its vapor dissolves in the saliva reaching the tastebuds. In certain situations in which the first nerve, the olfactory nerve, which carries the sensation of smell, is injured by disease, trauma, or is paralyzed, the sensations of taste are obtunded or absent and perception of different tastes is impaired (Refs. 1 through 4).

The four fundamental taste sensations are not aroused with equal intensity over all parts of the surface of the tongue. Each type of taste sensation is served by its own type of tastebud. Taste receptors sensitive to sweetness and to saltiness are most numerous at the tip and fore part of the tongue. Those responding to sourness are found along the edges of the tongue. The tastebuds sensing bitter tastes are scattered over the back of the tongue and epiglottis. Some substances, such as sodium salicylate, have a bitter-sweet taste. When sodium salicylate is first taken into the mouth it comes in contact with the fore part of the tongue and tastes sweet, then the bitter element comes into play when the substance passes the posterior part of the tongue. Little or no sensation of taste can be aroused from the central portion of the tongue surface (Refs. 1 through 4).

The sense of taste is much less sensitive than the sense of smell. Sweetness, for example, is detected in a dilution of 1 part in 200; saltiness in dilution of 1 part in 400; sourness due to acids in a dilution of 1 part in 130,000; and bitterness, such as would be induced by quinine, by 1 part in 2,000,000 (Refs. 1 and 4).

Several nerves carry taste impulses from tastebuds. Those that subserve the tongue are the chorda tympani branch of the facial nerve and the glossopharyngeal nerve. The chorda tympani nerve supplies tastebuds over the anterior two-thirds of the tongue; the glossopharynegeal nerve supplies tastebuds over the posterior third. The fibers of the chorda tympani nerve are conveyed to the tongue in a trunk of the lingual nerve which is a branch of the mandibular division of the fifth nerve. The vagus nerve carries impulses from the extreme lower posterior portion of the tongue in the hypopharynx and from the surface of the epiglottis. The center for taste lies in the lower end of the somesthetic area of the cerebral cortex.

d. *The physiology of smell.* Smell is very closely allied to taste and has been described as "taste from a distance." In many animals, the sense of smell is incredibly acute, and a large proportion of the brain is concerned with this sense. In some species, the sense of smell is of paramount importance because smell is relied upon to warn of the approach of enemies, to guide an animal in the quest of food, and to sense direction. Even in humans, in whom the sense of smell is comparatively rudimentary, certain substances, for example, some mercaptans, can be detected in a dilution of one part in 30,000,000,000 or more parts of air (Refs. 2 and 3).

An odorous material continually emits particles of molecular size which are carried in the air to the olfactory receptors. Substances which pass readily into a vapor state or exist in a gaseous state, such as turpentine, gasoline, chlorine, and some essential oils, generally have strong ordors. Nonvolatile materials, on the other hand, such as heavy metals, are ordorless. In order to be smelled, a substance must reach the nose in a gaseous form (Refs. 2 and 3).

The mucous membrane of each lateral wall (or side wall) of the nasal cavity covers three ridges which arise from the lateral bony wall of the nasal cacity (superior, middle, and inferior turbinate or conchae). The interior of the nose is thus divided incompletely on each side into four compartments or regions, each region placed above the other. The lower three of these regions serve as air passages. They communicate with the outside via the nostrils at the front and with the pharynz at the rear. The uppermost compartment consists of a narrow cleft lying immediately beneath the anterior portion of the floor of the skull. The receptors for smell (olfactory receptors) are imbedded in a small patch of mucous membrane situated on each wall of this narrow space.This narrow space is a blind pocket from which the main air currents are excluded. Air containing the odorous particles must, therefore, be carried to the olfactory mucous membrane if an odor is to be perceived. This is done either by diffusion or by convection currents that result when the cooler inspired air meets the warmer air within the nose. When, for example, one wishes to smell a particular scent, an individual makes a quick, short sniff. The sharp inhaling of the cool outside air creates ascending convection currents which are conveyed to the inside of the blind pocket, which is the sensitive area and contains the receptors. The material does not act directly on the olfactory receptors, but must first be dissolved in a layer of fluid covering the mucous membrane. The similarity between the sense of taste and the sense of smell in this regard is of interest (Refs. 2 and 3).

There is an infinite variety of odors, and it is difficult to satisfactorily classify the different types of odors. An attempt has been made to group them under eight headings: (1) Ethereal, (2) aromatic (resinous), (3) fragrant (balsamic), (4) ambrosial, (5) garlic, (6) burning, (7) goat, and (8) foul. The blending of these various types gives rise to the different degrees of a particular odor that may be sensed. The olfactory epithelium is composed of spindle-shaped nerve cells distributed evenly among elongated cells which are purely supporting in function. Each dendrite, after emerging from between the supporting cells, divides into a tuft of some six or eight straight filaments which project a short distance beyond the epithelial surface. These pass through the perforations in the floor of the skull and enter the olfactory bulb, a primary olfactory center. Olfactory receptors adapt quite rapidly, and they soon no longer respond to some particular stimulus. It is well known that an order, though strong when first perceived, becomes imperceptible after a short period of time. This phenomenon of adaptation also observed among other types of receptors is not due to fatigue. The receptors still remain active because when some particular odor is no longer perceived another odor is readily perceived when the subject is exposed to it. In some individuals there is an inability to smell certain odors at all, even though there is no impairment of the olfactory sense. For example, hydrocyanic gas, which is a poison used for the extermination of vermin, has an odor of bitter almonds which is strongly perceived by some individuals and quite odorless to a small segment of the population (Refs. 2 and 3).

References

(1) Taylor, N. B., "The Senses of Taste and Smell; Common Chemical Sense," *in* "The Physiological Basis of Medical Practice: A Text in Applied Physiology," edited by C. H. Best and N. B. Taylor, 8th Ed., Williams and Wilkins Co., Baltimore, pp. 423–428, 1966.

(2) Taylor, N. B., "The Senses of Taste and Smell; Common Chemical Sense," *in* "The Physiological Basis of Medical Practice: A Text in Applied Physiology," edited by C. H. Best and N. B. Taylor, 8th Ed., Williams and Wilkins Co., Baltimore, pp. 428–434, 1966.

(3) Best, C. H., and N. B. Taylor, "The Human Body: Its Anatomy and Physiology," 4th Ed., Holt, Rinehart, and Winston, New York, pp. 640–643, 1963.

(4) Best, C. H., and N. B. Taylor, "The Human Body: Its Anatomy and Physiology," 4th Ed., Holt, Rinehart, and Winston, New York, pp. 638–640, 1963.

e. *Absorption through mucous membranes.* Oral health care products are applied topically to the mucous membranes of the mouth, or throat, or both to exert their therapeutic effect. They are usually applied in the form of rinses, gargles, sprays, swabs, drops, lozenges, or powders (Ref. 1) Powders ordinarily are used on the teeth; occasionally, they are used on the mucus membranes. Ointments are seldom used in the mouth and throat. When they are used, they are applied with the finger or with an applicator. With the exception of lozenges and powders, the duration of contact of most preparations, particularly those formulated in aqueous, nonviscous media, is relatively brief, unless liquid preparations are formulated in solvents that adhere to the mucous membranes. Liquid preparations mix with the saliva and are diluted and swallowed. Some drugs combine with cell proteins and exert a therapeutic effect as long as the combination persists. Lozenges permit a more prolonged contact than rinses, sprays, or swabs and are, as a rule, more effective (Ref. 1).

Many drugs are absorbed readily from the mucous membranes of the mouth and throat and promptly pass into the systemic circulation (Refs. 1, 2, and 3). Although drugs used in the oral cavity are not intended to be swallowed, invariably all or a portion of a dose passes into the stomach or intestinal tract where it may undergo complete

absorption. Lozenges and powders ultimately are swallowed, and most of their components are absorbed either in the stomach or in the intestinal tract (Refs. 3, 4, and 5).

There may be considerable absorption of oral health care preparations from the mucous membranes of the mouth even though the contact is brief. The entire gastrointestinal tract, commencing at the oral cavity including the lips and ending in the rectum, is lined by a sheath of closely packed epithelial cells that form a continuous hollow tube from the mouth to the rectum. When a substance is absorbed it must first enter epithelial cells and be transferred across them to reach the fluid in the lamina propria beneath the cells and finally pass into the blood and lymph and into the capillaries. A substance may also pass into the lymph and then into the blood. The cell membrane is essentialy a double layer of lipid molecules between the which is stretched a layer of proteins and polypeptides. The lipid materials are oriented both inward from the interior of the cell surface and outward from the exterior of the cell membrane. The cell membrane is a continuous phase. It is perforated by minute pores through which hydrophilic molecules, including water itself, may pass as well as other small molecules such as urea, glycerol, and small ions such as chloride and potassium. Certain drugs readily pass through the mucous membranes; others do so with difficulty. Nonpolar substances can pass with ease, usually by simple diffusion. This selectivity is apparent rather than actual and is due to physical, chemical, and biologic factors involving the drug, the cell membrane, or both. Passage of a drug through membranes, often referred to as transport, is accompanied by processes which are either active or passive. Passive transport, such as simple diffusion, requires no expenditure of energy. On the other hand, energy is necessary for active transport since the substances are moved against a chemical or electrical gardient. For example, during the process of restitution of the nerve membrane to its normal resting (polarized) state after passage of a nerve impulse along a nerve fiber, the sodium ions must be forced out of the interior of an axon from an area of low concentration to the exterior where the concentration is higher. Energy is required to accomplish this movement of sodium ions from an area of low density to one of higher density. The chief mechanisms of drug transfer across the membranes are described below (Refs. 3, 4, and 5).

Diffusion through the lipid phase of the cell membrane varies with each drug. Nonpolar lipophobic, hydrophilic substances dissolve in the cell membrane and cross by diffusion. Nonlipid-soluble substances that are highly ionized do not readily traverse the lipid membranes of cells. Ions cannot penetrate cell membranes since they are not lipid soluble. Lipid-soluble polar substances readily penetrate the cell membrane by diffusion. The ease of passage depends upon the lipid-water partition coeffient of a drug. The partition of a substance between a lipid and an equal volume of water is important. The greater the amount of a substance that passes from an aqueous phase of a solution when shaken with an oily substance, the greater the partition coefficient and the greater its ease of penetration through cell membranes. Penetration of a polar substance is favored by a high lipid-water partition coefficient. Certain substances are polar in an acid medium and nonpolar in an alkaline medium or vice versa. In the presence of weak acids and bases, penetration is favored by the presence of a high proportion of lipid-soluble, nonionized polar form of a drug (Refs. 3, 4, and 5).

Intravenous injection of a drug that is poorly ionized is followed by a rapid accumulation of a drug in the capillary-rich organs, such as the brain, heart, liver, lungs, etc., since penetration occurs readily through the membranes. The reverse is true in the case of highly ionized drugs. For instance, quaternary ammonium compounds, which as a rule are highly ionized, will not penetrate the blood-brain barrier due to their poor lipophilic qualities. If the pH on the two sides of a cell membrane is different, the distribution of a weak electrolyte on each side of the membrane will also be different. Only the un-ionized form is permeable and will penetrate until the concentration on each side of the membrane is the same and an equilibrium is attained. The amount of ionized form present will depend on the pH of the medium in which it is dispersed. This is the case if the ionized form and the total concentration is less on the acidic lumen side of the gastrointestinal tract than in the neutral bloodstream. A weak acid present in the lumen of the bowel is rapidly absorbed and passes into the blood, whereas a weak base present in the bloodstream rapidly leaves the bloodstream and is excreted into the lumen of the bowel. It has been shown that a weak acid, such as aspirin, which is poorly ionized in the stomach, is rapidly absorbed from the stomach. On the other hand, ephedrine, which is a weak base and readily forms a salt with the hydrocholoric acid of the stomach and is highly ionized, is not absorbed (Refs. 3, 4, and 5).

A factor which also influences the distribution of drugs across membranes is their degree of protein binding. For example, aspirin is more concentrated in blood plasma than in tissue fluids because of the greater protein content of the plasma. One of the reasons why few drugs distribute evenly between the extracellular and intracellular fluid is that there are differences in protein content in the two media, and the protein-bound fraction is unable to traverse the cell membrane. There are also differences in the nature of proteins in the two media and in the affinity of a drug for the different types of protein which also account for the differences in concentration (Refs. 3, 4, and 5).

In summary then, the following factors are involved in the transport of drugs across membranes. (1) *The filtration through pores.* Hydrophilic, lipid-insoluble substances cross membranes through water-filled pores where there is a hydrostatic or osmotic pressure difference across the membrane. Water flows in bulk through the membrane pores carrying with it small molecules whose dimensions permit passage through the pores. The evidence that supports this is obtained by meauring diffusion rates. The passage of most hydrophilic substances depends upon their molecular size or molecular radius. Pores in the membrane may allow the penetration of molecules of small size, such as those of urea, into cells. Larger molescules not permeable through pores may pass across the capillary wall into the bloodstream. For example, the water that filters across the glomerular capillary membrane of the kidney carries with it the solutes of plasma (Ref. 3).

(2) *Facilitated diffusion.* Facilitated diffusion is dependent upon the concentration gradient but does not obey simple diffusion laws. An example of facilitated diffusion is the penetration of sugars through the red cell membrane. There is evidence indicating that these are dissolved in water and inward passage thereby is facilitated (Ref. 3).

(3) *Active transport mechanisms.* These are not dependent upon diffusion and may even resist it. Sodium ions present in a nerve after an inpluse has moved along its course must be extruded to the resting exterior to restore the cell membrane to its normal resting state. These ions must be pumped out of the interior of the fiber, where the concentration is low, to the exterior, and into the extracellular fluid

where the concentration is much greater. This involves a mechanism similar to pumping water up a hill. A characteristic feature is that it can be blocked by metabolic inhibitors which interfere with enzyme activity. It can also be inhibited competitively by other substances which utilize the same type of transport mechanisms. Active transport often shows specificity for particular types of chemical structures. The transport mechanism can become saturated when the concentration of the substances exceeds a certain limit and ceases. Other examples of such active transport involving metabolic energy in addition to the extrusion of sodium ions by nerve or muscle are the secretion of hydrogen ions by the stomach, the reabsorption of glucose by the tubules of the kidney, and the secretion of penicillin by the tubules of the kidney. Active transport is often visualized in terms of carrier mechanisms. The carrier may itself be an ion with a charge opposite to that of the ion to be transported. Specific carriers are responsible for the absorption of glucose and amino acids by the intestines. There are at least two carrier mechanisms in the kidney. One is for the secretion of acid compounds, such as penicillin and phenol; the other is for secretion of basic compounds containing the quaternary ammonium group or amines. Both the acidic and the basic mechanisms are competitive, so that the transport of one substance can be blocked by an excess of another substance in the same group (Ref. 3).

(4) *Pinocytosis.* This is a type of transport mechanism that involves the movement of substances, of large aggregates of molecules, or of large particles across cell membranes such as are found in emulsions and suspensions. It is an entirely different type of transport mechanism from all the others encountered. The cells engulf small droplets of an extracellular fluid. Pinocytosis can be observed in ameobae and in tissue culture cells. This probably occurs in mammals, also. Its role is poorly understood, but it has been suggested that it might be responsible for the uptake (absorption) of protein in the gastrointestinal tract of infants or for the absorption of liquid droplets in the alveoli of the lungs. It is doubtful that it plays any role in the absorption of drugs in the oral cavity or pharynx (Ref. 3).

Bioavailability of a drug is a term used to define the rate and extent to which a drug reaches the site of action after administration. In its most general sense, bioavailability refers to all methods of administration of drugs, e.g., orally, subcutaneously, intravenously, etc., and to any site of action. In practice, the term is most frequently applied to the oral administration of drugs and to the determination of blood levels after administration (Refs. 3, 4, and 5).

Absorption of drugs through the lining of the mucous membranes of the mouth and throat is similar to that of the gastrointestinal tract. These membranes behave as lipoidal barriers for the passage of drugs. The rate of absorption is determined by the proportion of nonionized drug present at the pH of the mouth, or throat, which is about 6, and by the drug's lipid solubility. Nonionizable lipid-soluble compounds such as nitroglycerin and various steroids are readily absorbed through the oral mucosa. The buccal route is especially advantageous for the administration of certain drugs which are acid-labile and are rapidly metabolized by the liver, since the acidic stomach and the portal circulation which carriers them to the liver are bypassed. High molcular weight compounds such as proteins, for example insulin, are not appreciably absorbed and may be largely destroyed by digestive processes in the mouth. Certain workers (Ref. 3) have developed a buccal absorption test in which the subject's mouth is rinsed for 5 minutes with a buffered drug solution which is then expelled and analyzed. They found that absorption could be entirely accounted for by the lipid solubility of the undissociated molecules of a drug. For example, at pH 9.2 over 70 percent of a solution of amphetamine was absorbed, whereas, at pH 6, none was absorbed. Absorption increased linearly with the concentration of the drug. There was no selectivity in the absorption of optical isomers of amphetamine, suggesting that absorption occurs by diffusion rather than by active transport (Ref. 3).

It was formerly believed that only a few exceptional substances, such as alcohol, were absorbed from the stomach. It is now known that drugs which are weak acids are absorbed to an appreciable extent from the stomach. Aspirin is practically undissociated at a pH 1 and, therefore, absorbed from the stomach. However, it is not readily absorbed from the mouth. If the gastric contents are made alkaline with sodium bicarbonate, the aspirin is not absorbed. Bases are generally not absorbed from the stomach because they form salts with the hydrochloric acid and are ionized.

Cutaneous barriers are more easily traversed by bases of drugs such as local anesthetics, etc., than by their salts. The penetration of bases through cutaneous barriers, however, appears to be limited, and not comparable to that occurring through the epithelial cells of the mucosa in either quantity or rapidity. Salts of most drugs are poorly absorbed or not absorbed from the skin (Ref. 2). Absorption of local anesthetics from the mucous membranes may occur rapidly (Ref. 6). Resulting blood levels simulate those following slow intravenous injection. The resulting blood level depends upon the area exposed (the anatomic site), concentration, and the total quantity applied. Furthermore, salts of local anesthetic drugs are as readily absorbed as the bases by the mucous membranes and cause a blockade. The anesthetic effect on the mucous membranes persists for some time after application, unlike the cutaneous responses, which promptly disappear after the drug is wiped from the surface. Absorption from the mucous membranes varies with the type of mucous membrane. A product may act twice as long on the conjunctive as it does on the tip of the tongue (Ref. 7).

The dissimilarity in absorption of drugs from the skin and the mucous membranes can be explained by histologic differences of these two types of epithelial coverings. Epithelial cells differ from each other in having an inherent tendency to make extensive mutual contact by means of small branches without cytoplasmic continuity. This characteristic has been referred to by Farquhar and Palade (Ref. 2) as the macular adherence. The epidermis varies from 0.7 to 0.2 mm in thickness, but is entirely devoid of blood vessels. Presumably, it is nourished by capillaries in the underlying connective tissue. The tissue fluids pass from the capillaries into an extensive system of extracellular channels and into the malpighian layers by simple diffusion (Ref. 2).

The mucosal tissues differ from cutaneous epithelium in a number of ways. In the mucosa there is no apparent separation of the epithelium from the corium except for a subepithelial membrane. Mucous membranes are more permeable than skin because they have no cornified layer to form a uniform barrier. Recent studies have revealed the presence of innumerable fingerlike protrusions from the mucosal cells that interdigitate with similar structures of adjacent cells. This results in a substantial increase in the area of the cell membrane surface of the superficial oral mucosa. A greatly enlarged absorbing surface facilitates drug penetration. The projection of these

basal cell processes into the corium and the absence of capillary basement membrane likewise favor rapid absorption of drugs from the mucosa. These observations explain, to a great extent, the greater degree of absorption of drugs from the mucous membranes than from the skin (Ref. 2).

Studies on the absorption of drugs from the oral mucosa indicate that diffusion plays a dominant role in absorption and that the lipid-water solubility coefficients are less important considerations. Whether the mucus and saliva significantly enhance absorption from the mucous membranes by acting as a spreading factor has not been established. Likewise, the pH of these surfaces may influence absorption of drugs since mucus and saliva may favor liberation of the base from the salts. The base is the active form, and the form that penetrates the mucous membrane. The rapidity of absorption of local anesthetics from the mucous membrane varies with the mucous surface studied. Peak levels of local anesthetics are attained most quickly after application to the mucous membranes of the tracheobronchial tree, less quickly after the anesthetics are applied to the mucosa of the mouth and throat, and least quickly after gastric and esophageal instillation. Blood levels may rise quickly after instillation of a drug in the posterior urethra, particularly if the surface has been traumatized by instrumentation. No significant absorption occurs from the bladder. No significant quantities are absorbed from the unbroken skin (Refs. 2, 6, and 7).

Vasoconstrictors added to local anesthetics injected perineurally retard absorption. They may not influence blood levels when combined with drugs used topically. Clinicians who use topical anesthetics regularly realize that reactions occur more often after topical application than after perineural injection. The occasional user, however, is often not fully aware of the hazards of topical application and is the one who most often encounters difficulty. Some of these drugs are potent and cause severe and often fatal reactions when they are absorbed from the mucous membranes. The Panel therefore has placed certain of these in Category II from the standpoint of safety (Refs. 6 and 7).

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 30–31, 1957.

(2) Farquhar, M. G., and G. E. Palade, "Junctional Complexes in Various Epithelia," *Journal of Cell Biology,* 17:375–412, 1963.

(3) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 49–59, 1976.

(4) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 44–46, 1965.

(5) Fingl, E., and D. M. Woodbury, "General Principles," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 3–11, 1970.

(6) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

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

4. *Symptoms for which OTC oral health care ingredients are used in the mouth and throat*—a. *Sore throat.* "Sore throat" is a symptom with many manifestations and with numerous causes. The term generally denotes pain (particularly on swallowing), discomfort, burning, or a scratchy sensation of the mucous membranes of the oropharynx or hypopharynx or both. A person having the symptom and describing it to others may convey as many impressions of what is being experienced as the number of persons to whom the symptom is described. Since the term is a general one and nonspecific, various adjectives are used to attempt to define it more clearly or describe it more accurately. Such adjectives as "mild," "minor," or "severe" are often used to describe the degree of discomfort. Such terms as "minor throat irritations" and "throat irritations" are likewise used to describe a sore throat (Refs. 1 through 4).

Sore throat is, in most cases, a manifestation of some systemic, infectious, or moninfectious disease. The Panel finds that many currently marketed oral health care products with sore throat claims are related to the common cold. The Panel recognizes the accepted use of these products by the consumer for treating cold symptoms. However, sore throat may also herald the onset of a serious, possibly fatal disease. Various viral diseases, such as measles, chickenpox, smallpox, and poliomyelitis, often begin with symptoms of the common cold, influenza, or incipient pneumonia, and are often accompanied by rhinitis (runny nose), cough, nasal congestion, fever, and other symptoms. Sore throat may be a symptom of serious diseases caused by bacteria, such as diptheria, scarlet fever, Vincent's angina, oral gonorrhea, or diseases caused by other organisms, such as secondary syphilis. It may be an early manifestation of aplastic anemia, agranulocytosis, or acute leukemia. Sore throat may also be due to local causes, such as swallowing irritating foods or drugs or an accumulation of thick viscous secretions from nasal or pharyngeal infections (postnasal drip). It may be due to fungal infection, such as candidiasis, resulting from use of topical antibiotics. it may also be due to the inhalation of irritating fumes, such as smoke, of noxious gases such as chlorine, or to the ingestion of concentrated solutions of caustic chemicals. Sore throat due to streptococcal infections may be followed by rheumatic fever or acute glomerulo nephritis. The Panel emphasizes that sore throat, "mild" as it may be, may often be a symptom of a condition which is amenable neither to self-diagnosis nor to self-treatment (Refs. 1 through 6).

The severity of the discomfort caused by a sore throat often depends upon the psychological response of the individual to the condition and its implication, particularly in reference to an impending illness. A sore throat developing on the first day of a vacation may have a different psychological impact than one developing at the end of the vacation. Such an individual is usually the one who resorts to self-diagnosis and self-treatment to obtain a "quick cure."

The cause, the extent, and the type of process causing the sore throat are important considerations. A slight reddening of the pharyngeal membrane may cause a "scratching" or a burning sensation in some persons and no symptoms in others. A localized infection in the oropharynx or hypopharynx or both may often be symptomless though this is rare. A pharynx that appears fiery and red may cause only a minor discomfort in some individuals and little or no pain, while it may cause severe pain in others. The Panel emphasizes that the factors involved in causing the sore throat are often of more importance than the degree of discomfort experienced. A slightly infected throat may be accompanied by runny nose, runny eyes (tearing), sneezing, cough, muscle aches, pain, fever, and gastrointestinal disturbances indicative of some type of systemic disease, usually a viral infection and, in many cases, of the "common cold." In certain cases of sore throat, particularly those due to organisms such as *Streptococcus pyogenes,* patches of exudate are

scattered over the pharyngeal mucosa. These discrete individual areas are painful in some persons and painless in others. An inflammatory process characterized by diffuse reddening of the mucous membranes, sometimes with an edematous appearance, may be more than a superficial process in the mucosa of the pharynx. Close examination often reveals that it extends into the deeper structures of the pharynx and involves the submucosal structures or superficial layers of muscles, the anterior and posterior pillars, or the muscles of the posterior pharyngeal wall causing marked discomfort on swallowing. The pain may even be referred into the nasopharynx to the areas of the Eustachian tubes, where it may cause earache. In cases in which the tonsils have been removed, an inflammatory process with or without exudate may be present in the tonsillar fossa and cause discomfort and pain (Refs. 1 through 6).

Sore throat may be due to acutely or chronically inflamed tonsils. In some cases, the process may proceed to abscess formation. Peritonsillar abscesses cause considerable pain and discomfort and often require surgical intervention. On rare occasions, the enlargement of one tonsil, accompanied by pain, has been due to a tumorlike growth. Since the tonsils are composed of lymphoid tissue, they may become enlarged and cause varying degrees of discomfort in cases of leukemia, Hodgkin's disease, and other types of lymphomas. Exudate from infections in the paranasal sinuses passing from the nasopharynx into the oropharynx or hypopharynx may cause sore throat by acting as a foreign body. The discomfort disappears when the exudate is removed (Refs. 1 through 6).

Sore throat may be due to trauma from foreign bodies such as glass, fish bones, or sharp pieces of bone that scratch the mucosa during swallowing when ingested with food. It may follow surgical procedures, such as tonsillectomy, biopsy, intubation, insertion of pharyngeal tubes, nasogastric airways, mouth gags, dental manipulations when the mouth is opened too widely from use of mouth gags, etc.

The Panel has gone to some length to enumerate these numerous causes and manifestations of sore throat to emphasize that sore throat is merely a symptom. In most cases, it is due to a self-limiting benign condition that recedes without treatment. In other cases, it cannot be ignored and medical advice must be sought. The Panel recommends that the term "sore throat" be used without qualification, as far as indications are concerned, as to its etiology and severity. However, it should be qualified by adequate warnings in the labeling.

Sore throat due to trauma is self-limiting and requires time for the healing process to occur. Anesthetic/analgesic-containing oral health care products may be helpful in these cases. Sore throat due to the accumulation of exudates may respond to agents that liquefy the exudate, or act as debriding agents and remove the exudates from the mucous membranes. Mucoid exudates that collect and cause discomfort can be removed by using sprays, or by irrigation with alkaline solutions. Pain can be relieved by applying topical anesthetics/analgesics in the form of sprays or in the form of lozenges which provide a continuous coating over an inflamed surface. The effectiveness of gargles in relieving discomfort due to sore throat is questionable because during the act of gargling the anterior pillars of the fauces approximate, the tongue rises, and the walls of the pharynx approximate. The action of the air stream prevents the access of fluid to the posterior pharyngeal wall. The various types of ingredients mentioned above for the relief of sore throat will be discussed individually later in this document.

References

(1) Brand, K. G., "Bacteriology: Basic and Applied to Otorhinolaryngology," *in* "Otolaryngology: Volume I, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 411–427, 1973.

(2) Schiff, G., "Viral Disease in Otolaryngology," *in* "Otolaryngology: Volume 1, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 428–442, 1973.

(3) Schwarz, J., "Mycoses," *in* "Otolaryngology: Volume 1, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 443–454, 1973.

(4) Ryan, R. E., W. E. Thornel, and H. Von Leden, "Synopsis of Eye, Ear, Nose, and Throat Diseases," C. V. Mosby Co., St. Louis, pp. 258–281, 1959.

(5) Stollerman, G. H., "Streptococcal Sore Throat," *in* "Cecil: Textbook of Medicine," 15th Ed., edited by P. B. Beeson, W. McDermott, and J. B. Wyngaarden, W. B. Saunders Co., Philadelphia, pp. 371–375, 1979.

(6) Gwaltney, J. M., Jr., "Pharyngitis," in "Principles and Practice of Infectious Diseases," edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett, John Wiley and Sons, New York, pp. 435–441, 1979.

b. *Sore mouth.* "Sore mouth" is a symptom which has many causes and which exhibits many manifestations. The term is used in this document to denote discomfort, a burning or scratchy sensation, or pain of the mucous membranes and other structures in the oral cavity. It may be generalized or localized. When localized it may involve the hard palate, soft palate, tongue, sublingual structures, frenulum, the buccal mucous membranes and the membranes on the inner side of the lip and the gingivae (gums). The Panel is not considering symptoms involving the teeth, periodontal structure, and gums since these have been reviewed by the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products.

The causes of sore mouth are numerous and varied and may be of a serious nature. Most of them are not amenable to self-diagnosis and self-treatment. As is the case with sore throat, sore mouth may be due to local causes or it may be a manifestation of a serious systemic disease. Sore mouth may be caused by trauma, burns, infections, neoplasia, metabolic disorders, developmental disorders, systemic diseases, and drug reactions. In addition, recurrent oral ulceration may occur including minor aphthous ulcer, major aphthous ulcer, and herpetiform ulcer (Ref. 1). The various causes of sore mouth are discussed in detail below to illustrate that few can be treated with OTC products. The following is an enumeration and discussion of the more obvious causes of sore mouth.

Trauma is one of the most common causes of sore mouth. It may result from injury from toothbrushing, from dentures, of from lacerations or abrasions from eating hard foods. Trauma may also be due to accidents from blunt force and other causes. The Panel is considering only minor trauma in this discussion and is excluding major trauma which occurs as a result of accidents in which there may be soft tissue injury and damage to teeth and jaws.

Trauma from the above causes may be mainfested by traumatic ulcers of the oral mucosa. Typically, these ulcers are linear with a gray, fibrinous exudate on the surface. Chronic ulcers of this type may show a considerable amount of induration of the surrounding tissue and may simulate squamous cell carcinoma. They may be difficult to distinguish from the latter on examination. Treatment with OTC products is usually not necessary since healing will occur following removal of the source of the trauma, e.g., dentures. A physician or dentist should be consulted when any ulcer persists for longer than 1 week.

Sore mouth may be due to chemical burns of the oral mucosa. Many chemicals and drugs may be caustic and cause burns in the mouth. Acids, antiseptics, kerosene, and numerous household substances may be ingested accidently and cause burns. There is cogulation of the surface epithelium, creating a necrotic slough with a white appearance. Healing usually occurs spontaneously without the use of drugs within 7 to 10 days. Some drugs may also cause burns. Aspirin (Acetylsalicyclic acid), phenol, trichloracetic acid, silver nitrate, and sodium perborate are examples of some that may do so.

Thermal burns of the oral mucosa are also a common cause of sore mouth. these arise from the accidental ingestion of hot foods and beverages. The anterior third of the tongue and the palate are the most common burn sites. Most of these burns are usually of little consequence and of relatively short duration. Burns may also result from inhaling flames, smoke, chemical fumes, and irritating gases, and may cause slough of the oral and pharyngeal mucosa. Fumes from ammonia, hydrochloric acid, chlorine, and other industrial chemicals may also cause burns of a similar type.

Sore mouth may be due to infections. Bacterial, viral, and fungal infections can occur in the oral cavity as well as in the throat (Ref. 2). Few of these are amenable to self-diagnosis and treatment with OTC oral health care products. The majority require diagnosis and treatment by a physician or dentist. Such infections are as follows:

(1) *Acute necrotizing ulcerative gingivitis (ANUG or NUG) (Vincent's infection).* This is one of the most common infections of the oral cavity and throat. It is characterized by the presence of interdental ulcers covered with a grayish exudate which bleed easily. Tenderness, malodor, fever, and malaise may be associated with the infection (Refs. 3, 4, and 5). Less commonly, a gingival flap overlying an erupting tooth, the palatal and buccal mucosa, or the oropharynx (Vincent's angina) may be affected. Antibiotics are usually necessary to relieve symptoms or eradicate the infections. The services of a dentist or physician are necessary for diagnosis and treatment.

(2) *Gonococcal lesions of the mouth.* These occur following orogenital contact (Ref. 6). The diagnosis and appropriate treatment can only be made by a physician.

(3) *Tuberculous lesions.* These are usually secondary to pulmonary tuberculosis, although it is possible that they can be of primary origin (Ref. 7). This type of infection is characterized by a chronic ulcer of the tongue or buccal mucosa. Self-diagnosis and self-treatment of such lesions is obviously not possible, and a physician must be consulted.

(4) *Syphilis.* Syphilis is a systemic disease caused by *Treponema pallidum.* It is most frequently acquired through sexual intercourse. An ulcer or primary lesion, known as a chancre, appears at the portal of entry. Syphilis is a systemic disease and occurs in three stages. Primary, secondary, and tertiary syphilitic lesions can occur in the oral cavity and result in a sore mouth (Ref. 8).

About 6 weeks after the chancre first appears, the secondary stage becomes manifest. It is characterized by a sore throat, and possibly sore mouth due to mucous patches. Generalized lymph node enlargement and skin rashes may also be present. The mucous patches are gray and translucent and are highly infective. Split papules at the angles of the mouth may occur that resemble angular cheilitis.

The tertiary stage of syphilis is characterized by the presence of the gumma which may occur intraorally as well as on other parts of the body. A gumma is usually characterized by a midline, punched-out lesion of the palate or tongue. Obviously this disease is not amenable to self-diagnosis and treatment with OTC oral health care products.

(5) *Primary herpetic stomatitis.* This disease is due to herpes simplex virus and is characterized by blisters on the cheeks, tongue, palate, floor of the mouth, and gingivae. The gingivae are frequently bright red, swollen, and bleed easily. These blisters rupture, leaving grayish-white ulcers with reddish borders which are painful. The infection is accompanied by fever. It is commonly seen in young children, and they may refuse to eat and drink because of pain. This type of infection requires expert care rendered by a dentist or physician.

(6) *Secondary or recurrent herpetic infections.* These infections are also due to herpes simplex virus. They are characterized by ulcerations which most commonly involve the hard palate. They may also appear on the lips. They cause discomfort characterized by a burning sensation or pain.

(7) *Herpangina.* This type of infection is caused by the Coxsackie group A virus. It is a relatively common disease of young children which occurs in mild epidemics towards the end of summer. Fever, intestinal upset, headache, and sore throat usually precede the appearance of tiny vesicles on the soft palate and pharynx. These ruptures leaving small ulcers with erythematous borders which also cause a burning sensation or pain. This type of infection requires professional attention and should be treated by a physician or dentist.

(8) *Candidiasis.* This is a fungal infection which is one of the most common afflictions of the oral cavity (Ref. 9). There are various strains of candida, but *Candida albicans* is still the most common causative organism of this type of infection (Ref. 10)

Infections due to candida may be either acute or chronic. The acute forms include acute pseudomembranous candidiasis (thrush) and acute atrophic candidiasis (Ref. 11). The chronic forms include chronic hyperplastic candidiasis and chronic atrophic candidiasis. Oral candidiasis is characterized by the presence of white plaques, or diffuse erythematous areas in the mouth. Infections due to candida can only be diagnosed by a physician or dentist using laboratory methods. Obviously candidal infections are not amenable to self-treatment with OTC oral health care products.

Angular cheilitis is an infection associated with denture stomatitis. Cohen (Ref. 9) states that the lesions of angular cheilitis are frequently infected by *Candida albicans* or coagulase-positive *Staphylococcus aureus.* In some cases both candida and staphylococcus are involved. The infection is characterized by fissures at the angles of the mouth that often heal without local medication. Obviously, the aformentioned infections are not amenable to self-treatment with OTC oral health care products.

There are several types of recurrent oral ulcerations. Among these are aphthous stomatitis, also know as recurrent aphthous stomatitis (RAS), and Behcet's syndrome. Aphthous stomatitis is not an uncommon cause of sore mouth. Lehner has applied the term "recurrent oral ulceration" to three varieties of recurrent oral ulcers (Ref. 1): minor aphthous ulcer (Recurrent aphthae of Mikulicz and Kummel, 1898) (Ref. 12), major aphthous ulcer (Periadenitis mucosa necrotica recurrens) (Ref. 13), and herpetiform ulcers (Ref. 14).

The minor and major aphthous ulcers are the most common of the three varieties. Both the minor and major aphthous ulcers are found in aphthous stomatitis and Behcet's syndrome (Ref. 15). The present evidence favors an immunological cause for both RAS and Behcet's syndrome.

These ulcerations result in various degrees of ulcers depending on their

location and extent in the mouth. They require diagnosis and treatment by a physician or dentist and are not amenable to OTC therapy.

Sore mouth may be an early symptom of oral cancer or other malignant lesions. Malignant lesions may make their first appearance as seemingly innocuous ulcerations or plaques such as leukoplakia. The lesion persists and enlarges. It may or may not be painful. Any ulceration or growth in the mouth, however small, that persists for more than several weeks should be examined by a dentist or physician. Many oral cancers are discovered by dentists. The Panel emphasizes that sore mouth may denote the presence of a serious lesion.

Anatomic aberrations due to developmental defects can result in sore mouth. Fissured or plicated tongue and erythema migrans (geographic tongue) can result in mouth soreness. Diagnosis and treatment of the disorder require the advice of a dentist or physician knowledgeable about oral diseases. Self-treatment with OTC products is not feasible.

Sore mouth may be a manifestation of certain blood dyscrasias. Blood dyscrasias include certain types of anemias (e.g., pernicious and aplastic anemia), the leukemias, agranulocytosis, and other leukopenias. These diseases are characterized by white cell deficiency and lower the resistance of the tissues and predispose to infections of the mouth which cause pain and soreness. In some anemias there is a loss of papillae on the dorsum of the tongue which induces soreness on the tongue. Lesions caused by these diseases can only be recognized and treated by a physician knowledgeable in hematology. None is amenable to self-treatment with OTC products.

Some systemic diseases are accompanied by lesions in the oral cavity that cause soreness or pain. Eruptive fevers, such as scarlet fever, smallpox, measles, and chicken pox, may cause oral lesions which cause sore mouth. The vesiculobullous diseases and certain generalized skin diseases, such as lichen planus, may also cause oral ulcers and the patient may complain of sore mouth. Obviously these diseases are not amenable to self-diagnosis, and the oral lesions are not amenable to self-treatment with OTC products.

Metabolic disorders such as chronic renal failure are characterized in their advanced stages by a rising blood urea and the clinical picture of uremia. Release of urea into the mouth via the saliva may cause stomatitis accompanied by sore mouth.

Diabetic patients are prone to develop sore mouth due to stomatitis because of the lowered resistance to infection. Self-treatment with OTC products may delay diagnosis, and the disease may progress to a serious state.

Deficiencies of certain vitamins such as vitamins C and B_{12}, minerals, and trace metals can result in sore mouth. Obviously none of these is amenable to self-diagnosis or treatment with OTC oral health care products.

Some drugs may induce systemic hypersensitivity reactions which are manifested by lesions in the mouth (stomatitis medicamentosa) and cause soreness in most patients. Some drugs used locally in the mouth can cause contact allergy (stomatitis venenata). Patients with stomatitis medicamentosa and stomatitis venenata usually complain of sore mouth. Such lesions are not amenable to self-diagnosis and treatment with OTC products.

It is obvious from the foregoing discussion of conditions that cause sore mouth that many are of a serious nature and rare and that, when compared to sore throat, the number that can be self-diagnosed and treated with OTC products is relatively small. Yet, sore mouth is common and occurs as frequently as if not more often than sore throat. In most cases it is due to minor ulcerations and other benign conditions that are self-limited and last only short periods of time. Therefore, there is ample justification for using OTC oral health care products for treating sore mouth. The anesthetics/analgesics offer temporary relief of pain and can be used as adjuncts to therapeutic regimens outlined by physicians in conditions where professional care is necessary. Debriding agents and expectorants may aid in the relief of soreness by facilitating removal of exudates which often coat these lesions. Demulcents and astringents may aid in relief of discomfort by providing a protective coating over a lesion, thereby reducing irritation due to external stimuli. As is the case with sore thorat, there is little if any evidence from controlled studies that the topical application of antiseptics is of any benefit in relieving these symptoms.

References

(1) Lehner, T., "Pathology of Recurrent Oral Ulceration and Oral Ulceration in Behcet's Syndrome: Light, Electron and Flourescence Microscopy," *Journal of Pathology*, 97:481–494, 1969.

(2) Meyers, B. R., and W. Lawson, "Infections of the Oral Cavity," *in* "Principles and Practice of Infectious Diseases," edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett, John Wiley and Sons, New York, pp. 466–480, 1979.

(3) Goldhaber, P., and D. B. Giddon, "Present Concepts Concerning the Etiology and Treatment of Acute Necrotizing Ulcerative Gingivitis," *International Dental Journal*, 14:468–496, 1964.

(4) Ratcliff, P. A., "Necrotizing Ulcerative Gingivitis," *in* "World Workshop in Periodontics," edited by S. P. Ramfjord, D. A. Kerr, and M. M. Ash, University of Michigan, Ann Arbor, MI, p. 377, 1966.

(5) Manhold, J. H., "A Pilot Experiment Employing Animals for the Study of Dental Psychosomatic Tenets," *New York Journal of Dentistry*, 28:343–344, 1958.

(6) Cohen, L., "A Synopsis of Medicine in Dentistry," 2d Ed., Lea and Febiger, Philadelphia, p. 17, 1977.

(7) Cohen, L., "A Synopsis of Medicine in Dentistry," 2d Ed., Lea and Febiger, Philadephia, p. 47, 1977.

(8) Cohen, L., "A Synopsis of Medicine in Dentistry," 2d Ed., Lea and Febiger, Philadephia, p. 16, 1977.

(9) Cohen, L., "Oral Candidiasis—Its Diagnosis and Treatment," *Journal of Oral Medicine*, 27:7–11, 1972.

(10) Budtz-Jorgensen, E., and U. Bertram, "Denture Stomatitis: I. The Etiology in Relation to Trauma and Infection," *Acta Odontologica Scandinavica*, 28:71–92, 1970.

(11) Cawson, R. A., and T. Lehner, "Chronic Hyperplastic Candidiasis-Candidal Leukoplakia," *British Journal of Dermatology*, 80:9–16, 1968.

(12) Mikulicz, J., and W. Kummel, "Die Krankheiten des Mundes," Verlag von Gustav Fischer, Jena, German Democratic Republic, pp. 46–47, 1898.

(13) Sutton, R. L., "Periadenitis Mucosa Necrotica Recurrens," *Journal of Cutaneous Diseases*, 29:65–71, 1911.

(14) Cooke, B. E. D., "The Diagnosis of Bullous Lesions Affecting the Oral Mucosa," *British Dental Journal*, 109:83–96, 1960.

(15) Cohen, L., "Etiology, Pathogenesis and Classification of Aphthous Stomatitis and Behcet's Syndrome," *Journal of Oral Pathology*, 7:347–352, 1978.

c. *Cough.* Cough is a protective mechanism designed primarily to free the upper and lower respiratory tracts of foreign objects, secretions, pus, and other materials. Ingredients that suppress cough are called antitussives. Cough and antitussives have been considered by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products because antitussives generally act systemically and are administered orally, parenterally, and by other routes. However, receptors that incite cough are found in the hypopharynx (laryngopharynx), and the possibility that they can be suppressed by topically acting drugs should be given consideration. The Panel, therefore, is including a discussion of cough and its suppression since there is a possibility that some of the ingredients evaluated may depress the pharyngeal receptors

and act as antitussives by a local action (Refs. 1, 2, and 3).

Coughing is produced by the rapid expulsion of air from the lung at high velocity following a deep inspiration and immediate voluntary closure of the glottis which is, in turn, followed by a sudden opening of the glottis and by a rapid forced expiration. Sounds of varying intensity and pitch are produced, depending upon the rate of flow of the exhaled gas, the total volume expelled, the tension on the vocal cords, and other factors that are responsible for the vibrations of the air waves that are interpreted as sound. Impulses that initiate the cough reflex may arise from many areas both within and without the respiratory tract (Refs. 1, 2, and 3).

Normally, coughing is produced by stimulation of sensory receptors of the glossopharyngeal and vagus nerves distributed in the mucous membranes of the lower pharynx, larynx, trachea, lung, pleura, and other areas of the respiratory tract. Stimulation of these receptors can be initiated by inflammatory processes, edema, chemical irritation, the presence of retained secretions, or foreign material blocking the upper and lower airways. Localized narrowing of the air passages may play an important role in stimulating receptors that induce the cough reflex. The act of coughing is coordinated by a group of neurons in the medulla called the cough center. These neurons can be depressed by certain drugs, particularly the central nervous system depressants such as the narcotics. Their activity can also be enhanced by certain chemicals and toxins, e.g., pertussis. Cough, in most instances, is under a considerable degree of voluntary control and can be initiated and self-suppressed at will within certain limits. Cough is active as a protective mechanism in healthy individuals, as well as those who are ill, for clearing the airway of any obstructing mucous secretions, or inhaled or aspirated foreign material.

The majority of medications that suppress coughing exert their effects systemically, although it is possible that some medications act locally as topical anesthetics, or by reducing inflammation or by decreasing edema. The Panel finds that the instances where this occurs are relatively uncommon. Preparations acting systemically are administered by mouth in the form of tablets, syrups, elixirs, or lozenges. Since the lower portion of the oropharynx and the hypopharynx are supplied by the ninth (glossopharyngeal) and tenth (vagus) nerves, it is possible for stimulation in these areas to induce cough. Cough originating by such local stimulation can be suppressed by topically acting agents such as anesthetics, decongestants, or anti-inflammatory agents. These can be administered topically in the form of lozenges or sprays. As far as this Panel is concerned, their action is local and not systemic. The Panel believes, however, that in the majority of instances stimuli that incite cough are widespread in the respiratory tract and only respond to systemically acting antitussives (Refs. 1 and 3).

Cough is frequently the apparent symptom of a wide variety of pathologic conditions, ranging from mild, self-limiting conditions to a serious and even fatal illness. In many cases, it can be tiring and debilitating, and its suppression is desirable. However, the cough reflex should not be suppressed indiscriminately, because it is important in preserving the function of the lung by maintaining an open airway (Refs. 3 and 4).

The "irritative cough" associated with self-limiting pharyngeal infections is usually viral in origin. It may also follow the inhalation of irritant gases, smoke, or dusts. The manifestations of these conditions are usually associated with a dry, hacking, nonproductive cough in which no sputum is expectorated. This type of cough lends itself to rational self-medication with systemically acting OTC preparations and does not ordinarily respond to products that act locally. On the other hand, secretions from "postnasal drip" exudates from inflammatory conditions in the nose and throat may incite cough receptors in an already irritated or inflamed throat and induce cough. The removal of these secretions temporarily relieves the cough. OTC preparations that facilitate removal of these secretions may relieve this type of cough. Drugs, such as narcotics and dextromethorphan that are systemically acting antitussives, exert no significant local effect and do not come under the purview of this Panel.

Any cough which becomes progressively worse after 7 days should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease (Refs. 1 through 4).

References

(1) Hunninghake, D. B., and J. D. Banovetz, "Systemic Drugs," *in* "Otolaryngology: Volume 1, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 479–480, 1973.

(2) Best, C. H., and N. B. Taylor, "The Human Body: Its Anatomy and Physiology," 4th Ed., Holt, Rinehart, and Winston, New York, p. 252, 1963.

(3) Jaffe, J. H., "Narcotic Analgesics," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 271, 1970.

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5. *Dosage forms of oral health care products.* All the ingredients reviewed by the Panel are applied to the surface of the mucous membranes of the mouth and throat to achieve their therapeutic effects by means of surface or superficial penetration. The therapeutic effect is a local one due to direct action on the structures beneath the mucous membrances. Since mucous membranes are effective absorbing surface, systemic actions frequently develop when drugs are applied topically to their surfaces. The topical route is often utilized to obtain systemic effects. The quantity of and rapidity of absorption of a particular drug through a mucous membrane may vary widely in different areas of the body. Absorption through the mucosa of the mouth and pharynx occurs readily. Pathologic changes in the mucous membranes may impede absorption of drugs and chemicals. The oral and pharyngeal mucosa is generally sensitive to and irritated by long-lasting drugs that remain in contact with the mucosa for extended periods of time (Refs. 1, 2, and 3).

Ingredients are applied to the mucous membranes of the mouth and throat by use of drops or powders, by gargling, rinsing, irrigating, swabbing, or spraying, or by slowly releasing a film of a drug over a surface by the use of lozenges. The use of ointments in the oral cavity is generally impractical due to their viscosity and difficulty in application. Lotions are also not recommended for use in the oral cavity. Combining a drug with a demulcent which adheres to a mucous membrane may prolong its contact with that membrane. The duration of contact of an ingredient depends on its chemical nature, viscosity, its reactivity with saliva and mucus, and its mode of formulation.

Washing out the oral cavity can be accomplished by rinsing or gargling. The duration of contract of a drug after rinsing, gargling, and irrigation with aqueous solutions is generally brief, and in most cases the therapeutic effect is of short duration unless the preparation is formulated with ingredients that prolong contact.

Sprays consist of hand-operated bulb-type nebulizers or aerosols. The nozzle of an aerosol spray should be calibrated so that the dosage can be metered in terms of seconds of use or the duration of the time of delivery. Dosage of drugs

from hand sprays can be calibrated according to the number of times a bulb is squeezed or the duration in terms of the time of delivery of an aerosol. The particle size of a droplet from a spray should be uniform and between 30 and 100 um in diameter. Otherwise baffling occurs, or the droplets pass into the lung and the spray does not reach the surface for which it is intended (Ref. 4).

Swabbing may permit more prolonged topical contact of an ingredient, particularly when combined with a demulcent to prolong contact. It is also believed that swabbing, even if done very gently, may produce some abrasions of the mucosa and by doing so may increase the absorption of an ingredient. Theoretically, the contact of an agent would be the same, regardless whether it is applied by spray or swab (with the exception mentioned above). The germicidal action of topical antiseptic antimicrobial agents is confined to the surface to which the drug is applied and to the debrided tissues. They may not be effective if contact is brief; however, this depends on many factors like adherence, the vehicle, etc. Living cells resist the penetration of effective concentrations of antimicrobial agents (Ref. 5).

Topical anesthetics penetrate the mucous membranes and pass into the nerve receptors in the mucosa where they may remain for a period of time depending upon their chemical and physical properties, such as lipid solubility, protein-binding capacity, and molecular structure to exert a sustained effect.

Mucosal surfaces that do not normally come into contact with water are generally irritated by it since water is not isotonic (osmotic irritation). This irritation can be avoided by using isotonic solutions (0.9 percent) of sodium chloride. Solutions in oil are also used to avoid osmotic irritation. Their immiscibility with the moisture of the mucosa prevents direct contact with the cells, and their actions, therefore, are slower but generally more prolonged. Oils, however, are undesirable since they may be aspirated and overuse may cause pulmonary irritation and fibrosis. Ointments make poorer contact with a mucous surface because viscosity limits their spread (Ref. 5).

The mouth and throat are usually treated by use of sprays, swabbing, irrigation, or the use of lozenges. The Panel is doubtful of the effects of gargling for treating symptoms affecting the throat. Medication in a gargle will not reach the throat unless the liquid is swallowed. The airstream in gargling might help to expel mucus, similar to clearing the throat. This topic is described in more detail below.

Nose drops, sprays, and other OTC preparations instilled into the nose pass into the pharynx and may exert a therapeutic effect in some cases and an adverse effect in others. For this reason a discussion of the nasal muscosa is mentioned here (Ref. 5). The nasal mucosa differs from that of the mouth and oropharynx in its response to drugs. Hypotonic and astringent solutions are less irritating than hypertonic solutions. Burning and other disagreeable sensations in the throat may follow the use of nose drops. Absorption in the nose occurs readily so that the local effects of drugs may occur quickly (Ref. 5).

The Panel has considered the various modes of application of topical products to be used in the oral cavity. Some examples of methods of application generally appearing on the labeling include "gargle freely," "spray freely," etc. The proposed labeling denotes the methods of application that are indicated for the various active ingredients, the dosage form, and the type of vehicle employed. Some preparations may be used in several different ways, as for example in the form of sprays, incorporated in the form of a lozenge, or prepared in the form of a rinse (Ref. 5). The accepted technique and directions for use appear in the labeling of the appropriate ingredient or combination statements discussed elsewhere in this document.

a. *Gargles and mouthwashes.* A gargle is a fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat. The gargle solution does not reach the throat unless it is swallowed. Gargling is accomplished by taking the fluid into the mouth and forcing expired air through it, while the head is tilted backward (Ref. 6). A gargle is intended for cleansing the throat, treating a diseased state, or relieving symptoms due to a diseased state of the throat. A mouthwash, or mouth rinse, also known as a collutorium, which may or may not be medicated or flavored, is a fluid used for cleaning the mouth or treating diseased states of the mucous membranes of the mouth. Actually the terms "gargle," "mouthwash," and "mouth rinse" merely denote how fluids are used in the oral cavity and give no indication as to what benefits may result from their use (Refs. 6 and 7).

Most mouthwashes are aqueous or water-alcoholic solutions in which are incorporated active therapeutic ingredients, pleasant-tasting flavorants, pleasant odoriferous materials, and various pharmaceutical necessities. The active ingredients present in these solutions are varied (Ref. 8).

The ideal solution used for a gargle, mouthwash, or mouth rinse should be one that is noninjurious to the normal tissues of the mouth and throat. It should be stable, composed of ingredients that remain in contact for the time required to exert the claimed therapeutic effect, and not be absorbed by the mucous membranes. It should be easily washed from the mucous membranes. It should be easily washed from the mucous membranes when the desired effect has been obtained and there is no longer any need for the drug to be in contact with the tissues. It should be nonirritating and nonsensitizing to tissues, pleasant tasting, pleasant smelling, and nontoxic if swallowed and absorbed from the gastrointestinal tract.

Unfortunately, the terms "mouthwashes" and "rinses" do not accurately define such preparations on the basis of composition, nor do they differentiate between therapeutic or cosmetic uses. Most mouthwashes are used for cosmetic purposes and consist of liquids with pleasant odors and tastes to rinse out the mouth.

The Panel regards gargles, mouthwashes, and mouth rinses that contain ingredients used for cleansing purposes, flavorings, or odorants, particularly those that are used on a regular basis such as one or more times daily and are not used to treat symptoms of a disease state of the mouth and throat, as cosmetics. The Panel emphasizes that OTC oral health care products for which a medicinal claim is made should be used only occasionally and for short-term therapy. This time limit should be designated on the labeling. The Panel does not regard oral health care products appropriate for use proplylactically to prevent the development of symptoms or disease states of the mouth and throat. The Panel recommends that any medicinal claims for "prevention" not be allowed.

The value of gargling in the treatment of sore throat is questionable (Refs. 8 and 9). This has been the subject of discussion in the literature for many years (Ref. 10). Tests performed with dyes and colored powders, such as charcoal black or radiopaque substances, followed by visualization by roentgenogram support the contention that in most cases, gargles may reach the anterior pillars but not the posterior pharyngeal wall or the posterior pillar (Ref. 10). They do not necessarily

establish physical contact of a medicine with a diseased surface of the pharynx. Contact is made in the oral cavity (Refs. 5, 8, and 12).

It is argued that many solutions used for gargling contain detergents that lower surface tension and enhance the ability of the liquid to penetrate into areas not accessible to water. This property facilitates penetration to convoluted areas of the tongue, mouth, and throat, aiding in debridement of these areas. It is also claimed that the physical act of gargling also creates an aerosol type of dispersion which aids in the spread of the solution and its ingredients throughout the mouth and throat.

It is the feeling of the Panel that these differences in conclusions drawn from studies concerning the effectiveness of gargles for use in the throat are due to numerous variable factors that enter into a study. During the act of gargling, the anterior pillars of the fauces approximate, the tongue rises, and the walls of the pharynx approximate. The action of the airstream prevents the access of fluid to the posterior pharyngeal wall. The gargle does not reach the throat. The airstream is directed away from the throat, preventing fluid from running back.

It is the consensus of the Panel that sprays are more effective for use in the throat, and the Panel recommends their use for products intended to reach the pharyngeal structures (Ref. 8). (See part II. paragraph B.5. below—Dosage forms of oral health care products.)

The absurd notion that antimicrobial agents in gargles, mouthwashers, and mouth rinses are necessary for daily cleansing of the mouth and throat is based upon tradition, promotional appeal by manufacturers, and misunderstandings concerning their effectiveness and safety rather than on well-documented facts (Ref. 11). The introduction of anti-infective drugs such as the chemotherapeutic agents, antibiotics, and other drugs possessing selective toxicity for a particular micoorganism or class of pathogenic microorganisms without harming the cells of the host has been responsible for relegating antiseptics for use in the mouth and throat into obsolescense. The selection of the proper antimicrobial agents manifesting selective toxicity for an offending organism can only be made by a practitioner of medicine or dentistry. The majority are administered systemically and not topically.

The Panel has reviewed and agrees with the findings of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group (DESI), which pertain to uses of mouthwashes and gargle preparations. In publishing a proposed statement of policy in the **Federal Register** of August 4, 1970 (35 FR 12411), the Commissioner of Food and Drugs stated:

> that there is a lack of substantial evidence that those preparations are effective for any of their labeled claims which relate to antimicrobial, antiseptic, germicidal, and analgesic uses.
>
> In addition to mouthwash and gargle preparations for which new-drug applications are in effect, there are many similar products on the market. The Food and Drug Administration has surveyed the labeling of such products and finds that many of them make direct or implied claims for benefit relating to antimircorbial, antiseptic, germicidal, or analgesic effects. Available information has been reviewed and has not been found to substantiate such claims.
>
> (c) The Administration will not object to labeling of a mouthwash, mouth freshner, or gargle preparation which offers it for such use as an aromatic mouth freshener (provided the product contains aromatic ingredients); as a refreshing mouth rinse; as an aid to daily care of the mouth, and for causing the mouth to feel clean. The label declaration or implication that an ingredient of such an article is active, when this is used to imply that the article has a prophylactic or therapeutic effect, may cause the article to be misbranded. However, an ingredient may continue to be listed on the label if it does in fact contribute to the nonprophylactic and nontherapeutic and usefulness of the article (e.g., wetting agent, foaming agent).

It is obvious that these claims are cosmetic and not therapeutic and that both the NAS–NRC study group and FDA regard mouthwashes as cosmetics. The Panel, from its evaluation of ingredients in oral health care products discussed below, likewise concludes that there are few, if any, indications justifiying the use of OTC mouthwashes, mouth rinses, and gargles containing antimicrobial agents for self-medication or for oral health care by lay consumers.

b. *Lozenges and gums.* Lozenges or troches, as they are sometimes called, are circular or oblong in shape. They are made by cutting, punching, or molding a flavored mass consisting of sugars, mucilages, gums, or bases of fruits, in which active therapeutic ingredients are incorporated. They are intended to be sucked, gradually releasing drugs into the saliva to act topically in the mouth and throat. They are made of varying consistencies depending upon the intended dissolution rate that is required to liberate the desired quantity of drug for the indicated therapeutic purpose (Ref. 13).

The therapeutic effectiveness of lozenges is difficult to evaluate because many variable factors may alter their performance during the conditions of use. Meaningful data from well-controlled studies on the effectiveness of lozenges are lacking because such data are difficult to obtain in patients. The composition, stability, consistency, size, rate of dissolution, taste, odor, and appearance of a lozenge are all important factors that enter into determining their effectiveness. There is no set of "average" conditions under which the effectiveness of a lozenge can be determined. The size and area of the mouth and throat, the surface area the drug is intended to cover, and the amount, the pH, and viscosity of the saliva being secreted all vary widely from one individual to the next and even in the same individual from moment to moment, modifying the action of the ingredients in a lozenge. Generally, a given dose in milligrams of each ingredient is incorporated in a single lozenge. The cohesion, the ease of aborption by the mucous membrane, the stability of drugs released from a lozenge, and the cause and type of lesion being treated are also important considerations. Drugs that are not soluble and not easily absorbed by the oral and pharyngeal mucous membranes pass into the stomach and may be absorbed there, acting systemically. The duration of action of drugs released from lozenges is generally short-lived and disappears as soon as the drugs are washed away by the salvia unless they penetrate cells and bind with proteins and other cellular constituents or are incorporated with demulcents that are tenacious and not easily washed away by the saliva. Their cohesion to the mucous membranes is generally unpredictable and of short duration, particularly if they are water soluble. Thus, in many cases if lozenges are to be effective they must be used frequently, usually in succession. As one dissolves, another must replace it if the active ingredients are to be of benefit.

Claims are made by some manufacturers that the effectiveness of some drugs released from lozenges may be two- or three-fold longer than the life of the lozenge. In some cases the Panel doubts that this claim can be made because the effect of the active ingredient is of short duration. The Panel doubts that benzocaine released from a lozenge can produce anesthesia for 3 or 4 hours when it finds that aqueous solutions of the same ingredient afford relief for less than 30 minutes.

Lozenges for use in the mouth and throat usually contain antimicrobial agents, local anesthetics, astringents, expectorants, demulcents, decongestants, debriding agents, or combinations of these.

The oropharyngeal symptoms which lozenges are intended to relieve are commonly due to local infection, ulcerations, congestion, and occasionally to irritation from drying of the mucosa, due to mouth breathing or from smoking. Most local infections, particularly in the throat, are viral or bacterial in origin. They are likely to resolve spontaneously. They can also be manifestations or prodromal symptoms of serious illness, particularly those in the throat, as is the case in various fevers, systemic viral infections, agranulocytosis, leukemia, diabetes, uremia, dehydration, and other such conditions. Infections can also be of fungal origin and respond to local treatment. However, the expertise and advice of a physician is required in such situations. OTC products are not appropriate for treatment in these conditions. They may, however, give symptomatic relief.

There is no evidence based on well-controlled clinical studies to support the effectiveness of lozenges which contain antimicrobial agents for OTC use. It is doubtful that they reach the microorganisms in the infected tissues. Effective broad-spectrum antiseptic agents not only kill the microorganisms but also damage the host cell. The Panel feels that such agents may do more harm than good. Furthermore, dilution by the flow of saliva and the poor contact with infected tissue make the use of antimicrobial ingredients in lozenges an inefficient method of applying such drugs locally. The medicines, as a rule, fail to reach infections in the furrows of the tongue, tonsillar crypts, and other inaccessible areas. Even if they do reach the areas, long-term clinical use attests to the fact that they are of dubious value in overcoming infections. A low concentration of an antimicrobial agent in the mouth can also encourage overgrowth of resistent bacterial organisms and fungal agents, such as oral candida, perhaps by altering the natural flora in the mouth (Ref. 14). If an antimicrobial agent is necessary to combat an infection such as a streptococcal sore throat, then one with specific activity, such as pencillin, should be taken orally or given parenterally and used under the advice of a physician. Though certain antimicrobial agents in lozenges may be helpful in treating certain ulcerative conditions, drugs that are effective systemically are preferred to those applied locally. Some antiseptics may irritate the mucous membranes and, likewise, some drugs, when applied locally, may also cause sensitization and at a later date cause hypersensitivity reactions if there is reexposure to the agent.

Lozenges containing local anesthetics often temporarily help relieve soreness in the mouth and throat and are worth using when this symptom is troublesome, provided the agent is able to reach the affected site and penetrate through the mucous membranes to exert its action on pain receptors. Benzocaine is one of the most widely used drugs for this purpose. Benzocaine can sensitize, but is seldom known to do so when used in lozenges. When patients are already sensitized to a drug after topical use on the skin or systemically, lozenges containing that drug can cause local hypersensitivity reactions when applied to a mucous membrane.

Aromatic flavorants or odiferous substances may increase the flow of saliva. Their vapor, if they are volatile, may produce a sensation which partially masks minor pharyngeal and nasal discomfort. Menthol, for example, stimulates receptors for cold, thereby producing the sensation of coldness which temporarily masks the pain. Menthol has a local anesthetic effect with a mean duration of 1.5 minutes and a mean latency period of 0.16 minutes (Refs. 15 and 16).

Demulcents incorporated in lozenges may relieve discomfort by coating irritated or inflamed mucous membranes and acting as protectants. Astringents incorporated in lozenges may act as protectants by coagulating proteins and may relieve symptoms. Debriding agents and expectorants, when incorporated in lozenges, may aid in the removal of phlegm, mucus, and debris, thereby relieving pain and discomfort. Decongestants incorporated in lozenges may relieve symptoms by shrinking mucous membranes and relieving congestion and by reducing swelling which is stimulating pain receptors.

The stability of ingredients and their chemical interaction with the "inactive" ingredients of a lozenge or a troche is of some concern to the panel. In one particular study, a formulation containing benzocaine was found to have lost half strength after 6 months in an unopened container (Ref. 17). Aspirin in certain formulations is hydrolyzed, and the odor of acetic acid is predominant when the container is opened. Phenol may be oxidized to quinones and be rendered ineffective. The shelf life of a lozenge, also, is of concern to the Panel. Not only does the Panel feel that the tenets of good manufacturing procedures be rigorously followed, but also that the shelf life of a product be indicated together with conditions of storage and other pertinent environmental factors.

Aspirin is incorporated in chewing gum supposedly to provide a topical action. In most cases the use of the gum is intended for slow release.

The Panel feels that the weight of the drug in milligrams per lozenge should be stated along with the total weight of the lozenge so that the consumers have all data and all facts pertaining to the concentration of drug in the formulation.

The following is a brief summary of the use of lozenges. Local anesthetic-containing lozenges may temporarily alleviate discomfort and soreness of the throat and are worth using when these symptoms are present. Astringents and demulcents may act as protectants and are also worth using. Debriding agents in lozenges alleviate discomfort by removing phlegm, mucus, and other debris. Effective expectorants may do likewise. Decongestants in lozenges decrease congestion of mucous membranes and alleviate discomfort due to inflammation or irritation. They may also retard the absorption of topical anesthetics and prolong pain relief. If a bacterial throat or mouth infection requires an antimicrobial agent, one with specific toxicity that acts systemically, such as an antibiotic, should be used.

References

(1) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Sanders Co., Philadelphia, pp. 49–59, 1976.

(2) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 44–46, 1965.

(3) Fingl, E., and D. M. Woodbury, "General Principles," in "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 3–11, 1970.

(4) Adriani, J., "Local Anesthetics," *in* "Chemistry and Physics of Anesthetics," 2d Ed., Charles C. Thomas Publishing Co., Springfield, IL, pp. 85–86, 1962.

(5) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, 8th Ed., W. B. Saunders Co., Philadelphia, p. 31, 1957.

(6) "Dorland's Illustrated Medical Dictionary," 25th Ed., W. B: Saunders Co., Philadelphia, p. 633, 1974, s.v. "gargle."

(7) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 30–31, 1957.

(8) Jaffe, J. H., "Narcotic Analgesics," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 271, 1970.

(9) Sollmann, T., "A Manual of Pharmacology and Its Applications to

Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 33, 1957.

(10) Minutes of the Advisory Review Panel on OTC Oral Cavity Drug Products, 12th meeting, October 16–17, 1975.

(11) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 823–824, 1947.

(12) Banovetz, J. D., "Topical Drugs—Basic and Applied," *in* "Otolaryngology: Volume 1, Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, p. 463, 1973.

(13) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 12, 1957.

(14) Kraus, F. W., "The Microbiology of the Oral Cavity and its Systemic Significance," *Dental Clinics of North America,* 2:309, 1958.

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

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

(17) Memorandum from J. Zaroslinski to R. Stoll in OTC Volume 130194.

6. *Recommended dose for oral health care products.* The Panel has defined and outlined below the general components of a dosage schedule for all products used in the oral cavity. The basis of the Panel's conclusions and recommendations are discussed in the general comments of each pharmacologic class and in the individual ingredient statements elsewhere in this document.

a. *Dosage range.* The Panel has examined the data submitted and concludes that, for purposes of clarity and accuracy, it is necessary to define the components of a dosage regimen. The components of a regimen for a particular product include a minimum effective dose, a usual single dose, a usual effective dose range, a maximum allowable single dose, and a maximum daily (24 hours) dose. These components of a dosage schedule are defined by the Panel in relation to a general OTC target population for which relief of symptoms is sought, such as minor pain due to sore throat, sore mouth, throat irritations, and antimicrobial activity.

(1) *Minimum effective dose.* The minimum effective dose is the amount of drug necessary to achieve the intended effect in some individuals in a significant OTC target population.

(2) *Usual effective dose.* The usual single dose is the amount of drug necessary to achieve the intended effect in most individuals in a significant OTC target population.

(3) *Usual effective dosage range.* The usual effective dosage range is the range between the minimum effective dosage and the maximum allowable single dose.

(4) *Maximum allowable safe dose.* The Panel finds that there may be circumstances when more than the usual single dose may be needed to provide an adequate effect. An increase in the usual single dose may be justified, for example, in individuals who, because of their age, body size or weight, or other factors, require a higher dose. The Panel defines the maximum single dose for most products as the maximum amount of drug that is safe and effective for use every 2 hours.

(5) *Maximum daily dose.* The maximum daily dose is the maximum amount of a drug that is safe and effective for use in a 24-hour period. Drugs that are sprayed or used as rinses or gargles may be absorbed through the mucous membranes or swallowed and absorbed from the gastrointestinal tract and thus produce systemic effects.

The Panel considers the adherence to a maximum daily dose necessary in the interest of safety. The clinical evaluation of some drugs clearly demonstrates side effects in the various organ systems and unwanted and sometimes dangerous symptoms. The maximum daily doses are indicated in the appropriate ingredient sections together with the adverse effects that can occur if these doses are exceeded.

C. Determination of Safety and Effectiveness

1. *Safety and effectiveness of ingredients for use in the oral cavity.* The Panel arrived at its conclusions and recommendations regarding the safety and effectiveness of all active ingredients after considering all pertinent data and information submitted. The Panel has adopted the following general guidelines:

a. *Safety.* The Panel's determination of the safety of single ingredients and combination products was based on the following criteria:

(1) The incidence and risk of adverse reactions and significant side effects when the agent was used according to adequate directions and instructions on the labeling.

(2) The potential for harm that might result from abuse or misuse under conditions of widespread OTC availability.

(3) Assessment of the benefit-to-risk ratio.

Ingredients and combination products that have been classed as Category I by the Panel require no further testing or evaluation for effectiveness or safety. Ingredients and combinations that have been classed as Category III for safety shall be subjected to testing outlined in the appropriate Data Required for Evaluation sections on Category III testing procedures. The manufacturer will be required to supply only the information that is missing and not all the information outlined in the section on testing.

b. *Effectiveness.* The Panel's determination of the therapeutic effectiveness of ingredients and combinations for use in the oral cavity was based on published and unpublished studies containing pharmacologic data considered by the Panel to be scientifically valid and pertinent. Clinical criteria for proof of effectiveness of a single agent or combination were determined by evaluating data from valid controlled studies, both subjective and objective, and by calling on the clinical expertise of the Panel members. These criteria will be discussed elsewhere in this document. (See paragraph C. of parts III., IV., V., VI., VII., and VIII. below—Data Required for Evaluation.)

Criteria for proof of effectiveness of the pharmacologic types of drugs evaluated were obtained from clinical studies which showed that an agent or combination caused a significant amelioration of the symptoms or provided a therapeutic effect for the stated indication in the labeling.

Ingredients or combinations that have been classed as Category III for effectiveness by the Panel shall be subjected to such testing as is required in the section on Category III testing procedures. Only that data which the Panel questions need be submitted unless the Panel concludes that the entire series of tests for effectiveness should be performed.

The majority of products used in the mouth and throat submitted to the Panel for review consists of combinations of active ingredients used together with pharmaceutical necessities listed as inactive ingredients. The remainder are single-entity active ingredients used with pharmaceutical necessities. The Panel recognizes that in order to be effective, the final product must be formulated properly and must conform to accepted pharmaceutical manufacturing standards. If not properly formulated, ingredients may not be bioavailable, or if they are bioavilable, they are present in less than the minmum effective dose or not in the form that exerts the intended therapeutic effects.

Important factors which the Panel considered in making its evaluations included the concentration of the active ingredients in the medium in which they are incorporated, the viscosity, the

volatility of the medium, the method by which the active ingredient maintains contact with the mucous membranes for the necessary length of time to assure a maximum therapeutic effect, the acidity or alkalinity of the medium, and the stability of the final product. Another important consideration to which the Panel gave weight was whether or not inert ingredients or active ingredients in a preparation interact or nullify the action of the principal active ingredients (Ref. 1). The designation of a pharmaceutical necessity as inactive or inert does not necessarily indicate that such an ingredient is chemically or pharmacologically inactive. An ingredient in a formulation containing more than one active ingredient could diminish the effectiveness of another ingredient by retarding its absorption in the mucous membranes or its passage into the lesion to which it is applied by altering the alkalinity or acidity of the medium and thereby changing the degree of ionization and its ability to penetrate epithelial barriers. The Panel also considered the effects of protein binding. Such binding could occur in such a manner that an ingredient would not be released to exert its claimed therapeutic effect or be absorbed (Refs. 1, 2, and 3).

The medium in which an active ingredient is incorporated not only must provide the necessary solubility and stability but also must maintain contact of the active ingredient with the surface upon which it acts.

References

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

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

(3) Gstirner, V., and R. Elsner, "Die Percutane Absorption der Salicylsaure aus modern Salbengrundlagen," *Arzneimittel-Forschung,* 14:281–286, 1964.

2. *Testing for recategorization of Category III ingredients.* When an ingredient or combination of ingredients is classfied as Category III because of insufficient data concerning its safety, effectiveness, or both, the manufacturer that produces such an ingredient or combination of ingredients must supply data to permit its reconsideration and reclassification from Category III to Category I. If such data are not available, the ingredient must undergo additional testing. The data submitted for reclassification should be available in the time period specified at the end of the description of each pharmacologic group. The Panel has indicated at the end of each section for each pharmacologic group protocols for obtaining data that are applicable to that particular pharmacologic group. General principles of the testing for reclassification applicable to all pharmacologic groups are outlined below.

The Panel considers the recommended protocols to be in agreement with the present state of the sciences of pharmacology and toxicology. The protocols suggested do not preclude the use of other newer, more refined laboratory or clinical investigative methods to establish safety or effectiveness of an ingredient. Manufacturers are expected to furnish only data relevant to unanswered questions in the ingredient sections or other sections of this document regarding the safety and effectiveness of the ingredients in their product. They are not expected to furnish all the data listed in the guidelines below.

Safety studies are required if the data submitted do not substantiate claims that an ingredient is safe when used as indicated in the labeling adopted by the Panel. Effectiveness studies likewise are required if the data submitted do not substantiate the claim that an ingredient or product is effective when used as indicated in the labeling adopted by the Panel.

a. *General considerations.* The Panel has categorized the ingredients it has evaluated in the following pharmacologic groups: (1) Anesthetics, (2) antimicrobial agents, (3) astringents, (4) debriding agents, (5) decongestants, (6) demulcents, and (7) expectorants. The ingredients of each category are grouped together, preceded by general descriptive introductory statements and followed by individual ingredient statements, labeling statements for the pharmacologic group, and data required for evaluation statements.

Certain general comments applicable to the preparation of protocols for the evaluation of all oral health care ingredients considered by the Panel are discussed below. Comments that are applicable only to a particular pharmacologic class and not to all OTC oral health care ingredients are considered at the end of the discussion pertaining to that particular pharmacologic group.

It is the consensus of the Panel that it is reasonable to allow 2 years for the development and review of evidence that will permit final classification of the safety and effectiveness of a Category III oral health care ingredient. The ingredients reviewed by the Panel and classified as Category III pose no serious problem or hazard for the consumer. Marketing need not cease during the time the product is undergoing testing. The Panel expects testing or reformulation to commece promptly. If data regarding adequate effectiveness and safety are not submitted within 2 years, the ingredients or a combination should no longer be marketed as an OTC product.

b. *Procedure for conducting studies on normal volunteer subjects and patients.* Investigational studies of a proper design should be conducted on human volunteers if reproduction of a particular lesion or oral cavity condition manifesting symptoms that are relieved as alleged in the labeling for indications is feasible (Ref. 1). Examples of experimental designs that may be appropriate and acceptable to the Panel include cross-over, double-blind, factorial, sequential trial, single-blind trial, and therapeutic equivalency studies (Refs. 2 and 3). Preference should be given to using double-blind studies with controls, so that the studies will demonstrate the effectiveness of the product. The cross-over technique should be used if possible. When used in a single-dose study, a period of 12 hours or more should elapse to allow elimination of an absorbed drug from the system. If repeated doses are used, longer periods of time should be allowed for such elimination. When the identity of an ingredient cannot be masked in performing a double-blind study and a suitable placebo is not available, control and treatment periods should be alternated if feasible. The control and treatment periods should be of sufficient duration to allow subjects to serve as their own control (Ref. 4).

A sufficient number of subjects should be use in such a study to permit statistical analysis of the data obtained (Ref. 1). The number of subjects tested should be sufficient to eliminated examiner bias, bias introduced by the placebo effect, and the effects of psychological responses to pain or to the symptoms in tested subjects. The subjects should be of both sexes and within the age groups for which use of the product is intended. The subjects should be healthy and free any ailment and should not be receiving any oral, parenteral, or topical medication. Female subjects should not be pregnant of menstruating (Ref. 4).

The study should be of sufficient duration to demonstrate effectiveness. The treatments should be performed on a random basis. The number and frequency of the applications of the preparation should be the same as

would be the case if the preparation were being used clinically. Any manifestation of local or systemic irritancy, sensitivity, or toxicity in these tests should be recorded and treatment discontinued.

When studies are performed in clinical situations, a large number of appropriate subjects with different types of oral cavity lesions or conditions presenting symptoms amenable to treatment by OTC oral health care products should be studied. Differentiation of patients should be made in accordance with the type and cause of a symptom. The randomization procedure should be used so that variables not otherwise controlled balance out (Ref. 5).

There should be detailed explanation of the criteria for assessment of the condition to be treated by the ingredient, of the method employed in testing, and of the validity of the method or methods used. Baseline demographic, medical, historical, and physical data for each subject should be obtained and recorded. Such data should include a medical history, a physical examination, laboratory studies, and other pertinent data (Ref. 6).

Studies should be performed on patients who have painful lesions, infections, or other afflictions in the mouth or throat that are amenable to treatment with OTC products. Subjects who have similar conditions and are being treated with a preparation should be divided into a treated group and a placebo group to obtain a controlled study (Ref. 7). Again, before-treatment data should be obtained and recorded. The degree of relief of symptoms, the onset of action, whether partial or complete, the duration of action, and the presence or absence of any rebound effect after the initial effect of the drugs wears off should be noted. A grading or scoring technique should be used to determine the degree of relief obtained from the symptoms being treated. The application of the product should be in accordance with the method outlined in the indication for use on the labeling. Tests should be performed using the final product formulation (Refs. 2 and 8).

The range between the minimum effective concentration and the maximal allowable (safe) concentration should be determined when lacking. This may be expressed in terms of the percent concentration of the preparation. Consideration should be given as to how the drug is absorbed or penetrates the mucous membranes, its duration of action, and its relationship to the length of time it remains in contact with a mucous membrane. Only the topical effect should be considered. The fact that a drug is absorbed and is detectable in the blood or is excreted into the urine in its pure form or as metabolites will not be accepted as evidence of effectiveness.

If not known, an attempt should be made to determine the possible mechanism of action or actions of the drug or drugs.

c. *Interpretation of data.* Detailed records should be kept. These should include legends, with specific explanation of codes, doses, mode, date, and time of application, the period of latency from the moment of application to the development of the desired therapeutic effect, the duration of the effect, the frequency of testing, and the duration of the test period. Investigative methods should be described in sufficient detail so that the experiments may be repeated by another investigator to verify and confirm results obtained from a particular investigator (Refs. 1, 2, 8, and 9).

Steps should be taken to eliminate examiner bias in both volunteer or clinical trials. Proper interpretation and explanation of the results should be provided. Whenever possible, statistical analysis should be employed to evaluate the results.

Positive evidence of drug effectiveness should be obtained from a minimum of two studies based on the results of two different investigators or laboratories.

All data submitted to FDA must present both favorable and unfavorable results.

d. *Safety evaluation.* Adequate, acceptable, controlled in vivo studies of acute and chronic toxicity in several species of animals should be supplied. The oral LD_{50} (mean lethal dose) in animals should be established and, if possible, the range of the toxic dose in man should be made available. This is important particularly since individuals, especially children, may accidently ingest an overdose or inhale excessive quantities of these medications (Refs. 1 and 10). Chronic toxicity studies of ingredients classified as Category III should be performed by two independent investigators (Refs. 11 and 12).

Tests for irritancy should be performed. These should include acute eye irritation, primary skin irritation, corrosivity, acute and subacute dermal toxicity, and sensitivity in animals (rabbits). Tests for topical irritancy on the oral and pharyngeal mucous membranes, including sensitization of the skin, and systemic sensitivity in man, should be performed if feasible. Methods for testing for irritancy and sensitivity are described below.

Data on systemic absorption, distribution, the metabolic fate, the rate of excretion, and possible cumulative effects should be supplied as discussed in the ingredient statements of this document.

e. *Recommended toxicological studies.* A variety of toxicological data can be obtained to demonstrate that a preparation is safe. Manufacturers are expected to conduct the applicable studies listed below. The Panel emphasizes that this requirement does not preclude the use of better testing methods which may be developed in the future. The Panel recommends that the following data be obtained in animals for the active ingredient(s) and for the formulation(s) intended for use on the mucous membranes of the mouth and throat.

(1) *Preclinical animal studies.* (a) Acute oral LD_{50} toxicity in rats.

(b) Acute eye irritation in rabbits.

(c) Primary skin irritation and corrosivity in rabbits or other suitable animals.

(d) Acute toxicity on the oral and pharyngeal mucous membranes in rabbits or other suitable animals (Refs. 11, 13, and 14).

(e) Acute toxicity of inhaled aerosols and sprays in rats or other suitable animals.

(f) Skin sensitization studies in rabbits and guinea pigs or other suitable animals.

(2) *Irritancy and sensitivity studies in humans.* A number of methods embodying the use of patch testing have been proven of value in determining skin irritancy and systemic sensitization. The Panel recommends that one of the following methods of patch testing be performed:

(a) The Draize human skin irritancy and sensitization tests or one of the various modifications may be used. The testing should be performed on the skin of the subject's back or arm (Refs. 1 and 15).

(b) The method of Shelanski and Shelanski (Ref. 16), in which the active ingredients or the formulation under study is applied at frequent intervals of 1 or 2 days to the test site for 3 to 4 weeks may be used. After a rest period of 2 weeks, a single dose of the drug or formulation is applied as a challenge (Ref. 16). The preliminary applications are made to detect primary skin irritants and provoke sensitization in susceptible individuals. The challenging dose detects whether or not the drug is a skin sensitizer.

(c) The maximization procedure of Kligman (Ref. 17) or one of its modifications uses an irritant which is

applied over a desquamated test site. Desquamation is performed by using a rubbing technique which facilitates penetration, thereby hastening and accentuating the skin-sensitizing potential of a substance (Ref. 17).

Solvents and other substances that are classed as inert ingredients used to formulate a finished product are indeed active in many instances and may penetrate the mucous membranes of the mouth and throat or can be swallowed. These are absorbed and detoxified or excreted in the same manner as the active ingredients. It is possible for highly lipophilic substances used daily for long periods of time to accumulate in the adipose and other lipid-rich tissues, particularly if they are not readily biodegradable. They may remain in the tissues for days, weeks, or months and produce chronic toxicity (Refs. 8, 9, and 18). However, none of the ingredients the Panel has evaluated are retained for long periods of time in adipose or lipid-rich tissues. Animal studies should be performed as a preliminary to human in vitro testing (Ref. 1).

The Panel recognizes that the clinical studies and studies on volunteers in the case of many ingredients will be subjective since objective methods are not available in many cases. This is applicable particularly to studies of preparations that relieve pain and discomfort. The Panel accepts such studies if they are performed according to the guidelines outlined above. The Panel also recognizes that certain ingredients have a dual action. An expectorant may relieve discomfort or soreness in the throat by acting both as a debriding agent and a detergent. The Panel accepts data for evaluation applicable to the principal action a drug manifests when such overlapping of action exists.

References

(1) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 21–47, 1976.

(2) Modell, W. H. O. Schild, and A. Wilson, "Applied Pharmacology," Amercian Ed., W. B. Saunders Co., Philadelphia, pp. 42–46, 1976.

(3) Mainland, D., "Some Statistical Problems in the Planning and Performance of Clinical Trials," *in* "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 27–35, 1964.

(4) Moyer, J. H., "Clinical Pharmacology: Objectives and General Considerations," *in* "Animal and Clincial Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 1–14, 1964.

(5) Irwin, S., "Variability in Drug Response," *in* "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 15–26, 1964.

(6) Moyer, J. H., "General Pharmacology: Objectives and General Considerations," *in* "Animal and Clincial Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 7–14, 1964.

(7) Beecher, H. K., "The Powerful Placebo," *Journal of the American Medical Association,* 159:1602–1606, 1955.

(8) Nodine, J. H., "Stages of Drug Evaluation in Man: General Principles of Experimental Design," *in* "Animal and Clincial Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 89–95, 1964.

(9) Brodie, B. B., "Kinetics of Absorption, Distribution, Excretion, and Metabolism of Drugs," *in* "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 85–88, 1964.

(10) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 37–42, 1965.

(11) Abrams, W. B., R. E. Bagdon, and G. Zbinden, "Techniques of Animal and Clinical Toxicology," *in* "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 55–67, 1964.

(12) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 26–36 and 53–55, 1965.

(13) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 26–36, 1965.

(14) Irwin, S., "Drug Screening and Evaluation of New Compounds in Animals," *in* "Animal and Clinical Pharmacology Techniques in Drug Evaluation," edited by J. H. Nodine and P. E. Siegler, Year Book Medical Publishers, Chicago, pp. 36–54, 1964.

(15) Draize, J. H., "Dermal Toxicity," *in* "Appraisal of Safety of Chemicals in Foods, Drugs and Cosmetics," The Association of Food and Drug Officials of the United States, Austin, TX, pp. 46–59, 1959.

(16) Shelanski, H. A., and M. V. Shelanski, "A New Technique of Human Patch Tests," *Proceedings of Scientific Section, The Toilet Goods Association,* No. 19:46–49, 1953.

(17) Kligman, A. M., "The Identification of Contact Allergens by Human Assy: III. The Maximization Test: A Procedure for Screening and Rating Contact Sensitizers," *Journal of Investigative Dermatology,* 47:393–409, 1966.

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

D. Labeling of OTC Oral Health Care Products

The Panel emphasizes the importance of specific informative and truthful labeling so that the consumer can select the most appropriate product for his/her condition and use it in the prescribed manner appropriate for obtaining the claimed therapeutic effect.

The Panel reviewed the general labeling requirements previously adopted by FDA for OTC products (21 CFR Part 201). These requirements provide for labeling information on the principal display panel of the packaging form, a statement of identity, the indications for use, the identity of ingredients, directions for use, other allowable information such as product performance or attributes, and general and specific warnings. The Panel concurs that these general requirements are appropriate for labeling of OTC preparations intended for use in the mouth and throat. The labeling of individual active ingredients will be discussed elsewhere in this document.

After reviewing all submitted labeling of OTC products used in the mouth and throat, the Panel recommends the following additional requirements:

1. *The statement of identity.* The statement of identity in the labeling of the product should contain the established name of the drug, if any, and should identify the product as an "oral health care product." It should also identify the pharmacologic class(es) of ingredient(s) contained within the product, i.e., antimicrobial, anesthetic, demulcent, astrigent, expectorant, debriding agent, or decongestant. When two or more active ingredients are combines and each is listed as an active ingredient, each ingredient shall be included in the statement of identity. The therapeutic action of a pharmarcologic class of an ingredient may not be used in the labeling indications described below because these terms do not denote the symptoms or disease process for which they are intended to be used.

2. *Ingredients.* The Panel concludes that products intended for use in the mouth and throat should contain only active ingredient(s) plus such inactive ingredients (pharmaceutical necessities) as are necessary for product formulation. All such drug products should also identify the active and inactive ingredients in the labeling by their established names. Terms such as "aromatics," "essential oils," and other vague connotations give no specific description of the identity of ingredients and should not be used. The Panel will,

however, accept terms that are specific and are actively descriptive, such as "oil of lemon," "oil of cloves," etc. Since the United States is slowly converting to the metric system, the Panel recommends that metric units be used in labeling.

The Panel concludes that the exact quantity of all active ingredients should be stated on the label in percent by weight or volume, in metric equivalents, and in the amount present in a unit dose by weight if the ingredient is a solid. If the active ingredient is a liquid, delivered in a unit dose, the amounts should be stated by weight or volume.

The Panel strongly recommends that the inactive ingredients also be listed on the label. "Inactive ingredients" are not necessarily inert and inactive and may cause drug interactions if ingested with other medications or cause toxic manifestations in cases of overdosage of the product. The Panel excludes from this requirement flavorants or coloring agents which are present in insignificant quantities.

The Panel believes that consumers are entitled to full disclosure of products used for self-medication and that each inactive ingredient should be stated on the label. The purpose each inactive ingredient serves in the formulation, such as for coloring, as a flavorant, or solvent, preservative, or vehicle, should also be stated in the labeling. These data are essential when poisonings are suspected, reactions due to hypersensitivity arise, or irritations develop. A minority of the Panel believes the quantity of the inactive ingreients should also be listed on the label.

The Panel concludes that therapeutic ingredients that are pharmacologically or chemically active in therapeutic concentrations can be designated by the term "inactive ingredients" only when they are necessary for proper formulation and are present in less than therapeutic concentrations.

It is the consensus of the Panel that the term "inert ingredients" be restricted to those ingredients that are chemically inert or insoluble in vivo and not absorbed by living cells. Examples are calcium sulfate, silica gel, and activated charcoal.

3. *Indications and directions for use* The indications for use of oral health care products should be simply and clearly stated, should provide the user with enough information for effective and safe use of the product, and should include the statement that the product is for the temporary relief of symptoms. No reference should be made or implied regarding the alleviation or relief of symptoms unrelated to a condition that is not an indication of the product.

The Panel recognizes that indication statements for oral health care products could be worded in a variety of ways and convey the same meaning, but for the sake of simplicity, clarity, and in the interest of minimizing consumer confusion the Panel recommends a restriction of indications for oral health care products. In addition, the Panel believes that limiting indications would protect the consumer from unfounded, misleading, and possibly hazardous claims. It would also eliminate similar products having different indications. The Panel concludes that the consumer would greatly benefit from such labeling.

The directions for use of oral health care products should be clear and provide the user with a reasonable expection of the results the product produces. The directions should be as detailed as possible and placed conspicuously on the label. The Panel would like to emphasize that the quantity of a product that is used, its mode and frequency of application, and its duration of contact with or over the area in which the symptom is located are all important considerations and have a definite bearing on the effectiveness of a product. Therefore, the Panel recommends that careful consideration be given to development of directions for use for oral health care products.

a. *Category I indications*—(1) *For anesthestics/analgesics.* "For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(2) *For astringents.* "Aids in the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(3) *For debriding agents.* "Aids in the removal of phlegm, mucus, or other secretions in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(4) *For demulcents.* "Aids in the temporary relief of minor discomfort and protects irritated areas in sore mouth and sore throat."

b. *Category II indications.* Labeling for OTC oral health care products should be symption oriented and not disease oriented. Labeling statements should not suggest or imply a cure or amelioration of a disease process or list a disease entity for which a product is not effective. The Panel believes that consumers with specific diseases or pathologic lesions should be under the care of a physican and that labeling referring to diseases that require medical intervention may mislead the consumer. Labeling of this type could encourage self-diagnosis or self-treatment of conditions not amenable to OTC therapy. Self-medication may lead to the progression of a disease process particularly if taken in inadequate doses or intermittently for pain relief or other conditions over prolonged periods of time by individuals who have persistent symptoms. In addition, any reference to pharyngitis, glossitis, tonsillitis, gingivitis, aphthous ulcers, or Vincent's infection in OTC oral health care product labeling is unacceptable to the Panel.

The Panel concludes that claims that state or imply that the prophylatic use of an OTC oral health care product maintains a healthy state in the mouth or throat are misleading to the consumer. Therefore, the Panel recommends that any medicinal claims for "prevention" not be allowed.

The Panel recommends that indications not recognized by the medical community be placed in Category II. For example, the Panel does not know what is meant by such indications as "irritable throat," "soothing lubricant," and "relieves stomatitis" and believes that consumers would also have trouble comprehending them.

The therapeutic or pharmacologic class of an ingredient, such as expectorant, anesthetic, or astringent, should not be used in the labeling indications because they do not denote the symptoms for which they are intended to be used. Cosmetic claims are not acceptable as indications for OTC oral health care products.

The Panel has placed in Category II those indications that are not supported by scientific data or sound theoretical reasoning or are inaccurate, misleading, or make claims that exceed those allowed for OTC products. The indications that the Panel recommends be in Category II are listed in the Category II labeling sections of each individual pharmacological group of ingredients.

c. *Category III indications*—(1) *For antimicrobials.* "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth."

(2) *For decongestants.* "Aids in the temporary relief of occasional discomfort due to congestion in the mouth and throat."

(3) *For expectorants.* "Aids in the removal of secretions and in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(d) *Claims deferred to other Panels.* Certain labeling claims have been deferred to other panels or to FDA for review since these claims involve anatomic areas other than those defined

as the boundaries of the Oral Cavity Panel; therefore, the claims are not within the scope of this Panel. The following claims have been deferred to the appropriate panels for consideration:

"Gum massage," "Prevents infection in burns, abrasions, minor cuts, open wounds, scalds, skin irritations, and sunburn," "For soreness or discomfort caused by denture irritation following tooth extraction or other minor gum irritation," "Temporary relief of pain and discomfort following periodontal procedures and minor surgery of the mouth," "For management of body odor or repair of gum tissues," "Relief of discomfort, deodorization, and minor gum disorders," "Before and after gingivectomy or curettement," "After extractions and under immediate dentures," "To promote healing and to relieve itching and discomfort and deodorization in minor wounds," "Burns, surface ulcers, cuts, abrasions, and dentures," "Indigestion relief," "For fast temporary relief of nasal congestion," "Fast temporary relief of nasal congestion and minor throat irritation," "Relief of postnasal drip, gum irritation, and sinusitis," "Promotes needed expectoration," "For fast temporary pain relief of minor denture irritation, toothache, teething, and cold sores," "Fast pain-relieving antiseptic for sores, cuts, burns, insect bites, fever blisters, and cold sores," "Relieves irritated gums, athlete's foot, poison ivy, poison oak, and itchy bites from chiggers, mosquitoes, and flies," "Relieves pain from minor injury, such as minor cuts, burns, scratches, abrasions, razor nicks, chafed or irritated skin, and painful sunburn," "Helps to prevent the spread and reinfection of acne," "Breathe easier when nose is clogged due to cold, hay fever, sinusitis," "Pain-relieving antiseptic for athlete's foot," "Dry dressings," "Prickly heat," "Refreshing for hot, tired, perspiring feet," "For dry dressings and prickly heat," "Combats infections, soothes pain, and promotes rapid healing," "For superficial wounds, cuts, minor burns, cold sores, fever blisters, poison ivy, sunburn, and chafed skin," "Soothes, cools hot irritated skin of prickly heat."

4. *Warnings.* The Panel recommends that additional statements be included in the labeling of oral health care products for proper use and adequate consumer protection. These statements are listed under the general headings of warning statements.

The Panel agrees with the current regulation (21 CFR 330.1(g)) containing the general warning statements, "Keep this and all drugs out of the reach of children" and "In case of accidental overdose, seek professional assistance or contact a posion control center immediately." The Panel considers these to be reasonable and proper statements for all OTC medications. Specific warnings or precautions that alert potential users of possible serious side effects of therapeutic doses, drug interactions, and especially the sequence of reactions due to overdose or drug interactions will be described in the discussion of each pharmacologic class or in individual ingredient statements elsewhere in this document.

The Panel also concurs with the recommended warning in the regulations (21 CFR 369.20) pertaining to throat preparations for the temporary relief of minor sore throat which states: "Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician."

Because OTC products may be purchased by anyone, the Panel is concerned that the public generally does not regard OTC products as medicines which, if used improperly, might result in injurious or potentially serious consequences. The public must be made aware of the concept that these products, like all medicines, carry some risk and should be used only as directed for the temporary relief of symptoms and not indiscriminately. The Panel, therefore, concurs with the FDA and considers it prudent to include the general warning statements now required by § 330.1(g) (21 CFR 330.1(g)).

The consumer should be informed of any possible signs of known toxicity, adverse reactions, or any warning requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe symptoms become apparent or the condition worsens. For example, one of the first symptoms of iodism due to overuse of iodine-containing compounds is stuffiness of the nose. (See Part IV. B.3.n. (1) below—Safety.)

Specific warnings that pertain to an ingredient appear below and in the discussions of individual ingredients. The consumer should also be warned of possible drug interactions that might occur when a product is taken concomitantly with other OTC products or medications prescribed by physicians. Such labeling should be conspicuously placed so that it will not be overlooked by the consumer.

The following are general and specific warning statements recommended by the Panel for use in the labeling of OTC oral health care products:

a. *Statements for use in the labeling of all OTC oral health care products.* (1) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(2) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

b. *Statements for use in the labeling of OTC oral health care products as specified*—(1) *For products containing phenylephrine hydrochloride or phenylpropanolamine hydrochloride.* (i) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(ii) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(2) *For products containing aspirin.* (i) "Do not use if you are sensitive or allergic to aspirin."

(ii) "Do not use if you have a bleeding problem or if you are on anticoagulants."

(iii) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(iv) "Do not use after surgery in the mouth or throat."

(v) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

(3) *For products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

(4) *For products containing glycerin.* "Do not use full strength. Dilute with two or three volumes of water."

5. *Labeling of product attributes.* The Panel accepts the use of terms that describe certain physical and chemical qualities of OTC oral health care products that are indicative of product performance so long as none of these terms implies that it is an indication that the product exerts a therapeutic effect, e.g., "pain reliever," "astringent," "demulcent," etc. The attributes described must pertain to product performance or to the pharmaceutical attributes of the formulation. The properties described may be due to the effects of colors, taste, or smell of specific inert or inactive ingredients

included in the final product formation. Such product characteristics in the labeling must be placed apart from the "indications" but must be in a conspicuous part of the labeling so that the consumer will be fully aware of their existence. Such labeling may be intended to make the product more appealing to the consumer. The Panel stresses that the terms used in such labeling must be carefully selected so that they do not imply that they exert any therapeutic effect or relieve any symptom, temporarily or permanently, or that they ameliorate a disease process or exert a curative effect.

The use of medicinal odors has been associated with the practice of medicine and pharmacy since the art of therapeutics was first conceived. This is of particular importance in oral health care products since smell and taste are closely associated. Although many chemical and instrumental methods have been used to measure quantities of substances emanating from the body that cause specific ordors, the cosmetic and pharmaceutical industries often rely on the personal reactions of trained individuals using subjective methods in making such assessments and measurements.

More important than color and odor is the matter of the taste of a product, particularly one intended for OTC use. The listing of flavorants and essences that are used for disguising odors and the fact that flavors of certain medicines are in official compendia attest to the acceptability of the practice by the community, the pharmaceutical industry, and the consumer of using these agents. Flavors that sweeten a final product containing a bitter ingredient are especially important. Description of the flavor in the labeling is particularly important when a product is formulated with several different flavors (i.e., cherry v. orange v. lemon) because one flavor may appeal to one consumer and not to another.

The Panel concludes that the practice of using descriptive labeling is both reasonable and informative to the consumer and not objectionable because it actively reflects inherent characteristics and the performance of the marketed product. Terms such as "does not stain," "pleasant tasting," and "non-oily" are acceptable. The Panel finds any claims related to product performance that cannot be substantiated by scientific data unacceptable. Labeling containing phrases such as "acts fast," "gives quick relief," "long-acting," "remarkable," or "acts promptly" is misleading and may be confusing to the consumer and is not permitted unless such claims can be supported by adequate scientific data.

E. Adverse Reactions

Most ingredients used in oral health care preparations are absorbed from the mucous membranes of the mouth or throat and pass systemically into the blood stream. They may be swallowed deliberately, as is the case when lozenges are sucked slowly over a period of time, and pass into the gastrointestinal tract, where they are absorbed and circulate systemically. In many cases absorpotion from the mucous membranes of the mouth and throat is more rapid than from the gastrointestinal tract. Ingredients may be absorbed in sufficient quantities during even a brief rinse or during gargling to produce systemic effects (Refs. 1, 2, and 3).

Certain oral health care ingredients produce unwanted or adverse effects regardless of how they are administered. Adverse effects to drugs are generally categorized as acute overdosage, chronic overdosage, secondary effects, intolerance, idiosyncrasy, local irritancy, local hypersensitivity, and systemic hypersensitivity (allergic) reactions. Side effects are not adverse reactions but are sometimes erroneously classed as such. Adverse reactions may be local or systemic or a combination of both (Ref. 4).

1. *Overdosage:* Overdosage, often referred to as acute toxicity, may occur after taking a single dose that is in excess of the therapeutic dose, by accumulation after repeating therapeutic doses at frequent intervals, or by deliberate ingestion of massive doses. Overdosage is usually manifested as an exaggerated form of the pharmacologic action or actions typical of the drug. However, ingestion of massive quantities may produce symptoms in addition to the exaggeration of the pharmacologic action typical of the drugs. The acute manifestations and residual effects of overdosage vary with each drug. The symptoms and severity are often dose-related (Refs. 4 and 5).

Gross overdosage may result in toxic and, in some cases, fatal reactions. Ingestion of massive quantities of some drugs may produce coma, cause convulsions, paraplegia, respiratory failure, hemorrhagic states, and other effects not ordinarily characteristic of the drug (Refs. 4 and 5). Phenol, in toxic doses, may cause convulsions and respiratory failure. The manifestations of overdosage of oral health care products are described in the ingredient statements under the sections on safety.

2. *Chronic overdosage.* Chronic toxicity may result from prolonged usage of the usual recommended doses or by repeatedly using subtoxic doses. Such usage may result in cumulative effects of the drug or its metabolites in the tissues and, in most cases, will present manifestations different from acute overdosage. Chronic exposure to or prolonged usage of a drug that ordinarily causes no ill-effects after several usages may produce irreversible changes in some organs. Antiseptics containing organic mercury permanently damage the kidneys. Chronic usage of phenolic compounds may result in cellular changes, discoloration of the skin, etc. (Refs. 4 and 6).

Chronic, long-term usage or overusage and its resultant manifestations are extremely important when considering OTC oral health care preparations, particularly gargles, rinses, or sprays, containing active ingredients such as quaternary nitrogenous compounds, iodophors, and phenolic compounds which are used on a day-to-day basis for weeks, months, or years at a time (Refs. 7 and 8).

Manifestations of chronic toxicity may often be delayed. This is sometimes referred to as remote toxicity. The remote toxicity of many of the newly added drugs, such as the "quats," is not known.

3. *Side effects.* The term "side effects" refers to one or more therapeutic effects that a drug may possess in addition to the principal therapeutic effect. Few drugs have a single pharmacologic action and considerable overlapping of actions is found among drugs. For example, the "caine" type of local anesthetics, such as procaine, manifests some antihistaminic and anticholinergic activities. These side effects are not harmful, but are often unwanted. The dryness of the mouth and visual disturbances caused by anticholinergic drugs, the drowsiness caused by antihistamines, and the pressor effects caused by vasoactive adrenergic drugs used as decongestants are examples of side effects that may not be harmful but are unwanted in some instances and desirable in others (Ref. 4).

The term "side effect" actually has no specific pharmacologic connotation and is not synonymous with the term "adverse reaction." It is sometimes used deceptively to convey the impression that an adverse effect is not necessarily undesirable, unpleasant, or harmful. Dryness of the mouth is desired and sought when an anticholinergic drug is administered to prevent formation of an excessive secretion of saliva, but unwanted when an anticholinergic drug is used as an antispasmodic or bronchodilator.

A true adverse effect of a drug differs from a side effect in that the adverse effect has no therapeutic usefulness, is undesirable, and may even cause harm. Nausea caused by gastric irritation following the use of an oral antibiotic would be an example of a true adverse effect. It is neither wanted nor is it therapeutically useful (Ref. 4).

4. *Secondary effects.* Secondary effects are indirect effects that occur during or after the use of a drug and do not result from any direct action of the drug itself on a particular organ system. An example would be the use of certain antimicrobial agents in the oral cavity that alter the normal bacterial flora and cause an overgrowth of symptom-producing pathogenic bacteria, or fungi, such as candida. The antimicrobial agent itself plays no direct role in accelerating the growth of such organisms but alters the environment and favors their growth (Refs. 4 and 6).

5. *Intolerance.* "Intolerance" is a term that describes a lower-than-the-average threshold to an anticipated response to a drug. The response is one normally expected of a drug, but the dose required to elicit that response is much less than is necessary to affect a significant group of a target population. Thus, a preparation containing an ingredient in a dosage form that ordinarily produces the usually anticipated response in a target population would cause an exaggerated response in a susceptible person exposed to the usual effective dose. Since many ingredients used in oral health care products are readily absorbed through the mucous membranes, intolerance may be encountered, although this is uncommon. For example, 10 milligrams (mg) of phenylephrine in a lozenge causes no pronounced pressor effect. In an intolerant individual it could produce a pronounced hypertensive response. Tolerance to a drug is often dependent upon a patient's physical condition (Ref. 5).

6. *Idiosyncrasy.* "Idiosyncrasy" is a term used to denote a qualitatively abnormal and unanticipated reaction produced by a drug in a particular, isolated individual in a target population. The reaction is not one ordinarily anticipated from use of the drug and is not one for which the drug is used therapeutically. A decongestant causing hypotension, instead of a pressor effect, or an analgesic causing hyperanalgesia or antianalgesia (exaggeration of a pain) would be examples of idiosyncrasy or idiosyncratic reactions (Refs. 4 and 9).

The term is often used erroneously to indicate that a reaction is due to hypersensitivity or an allergic state. The mechanisms involved in producing an idiosyncratic reaction and an allergic response are distinct and separate. The distinction is discussed in detail below. Ingredients used in oral health care products occasionally cause idiosyncrasy, but such reactions are uncommon. Aspirin in gum may cause an asthamtic attack in a nonallergic individual which could be ascribed to idiosyncrasy. The response is not immunogenic but is due to some interference with prostaglandin synthesis. In others who are truly allergic, the response is immunogenic in origin. The reaction would then be classed as sensitivity. Aspirin can cause both types of adverse reactions.

7. *Local irritancy.* Some ingredients in oral health care products possess the propensity for producing local reactions. Among these reactions are "irritation" of the mucous membranes (Ref. 10). Ulceration in the mouth or throat may appear after one or more applications of an ingredient when none existed prior to its use. This type of response is due to a direct irritating effect of an ingredient on the mucosal and submucosal cells. Caustic agents, such as phenol, cresol, and certain astringents, may have locally irritating effects. Locally applied aspirin tablets or aspirin-containing gums have produced aspirin burns. In some cases, the irritating response may appear early, sometimes immediately after application of a preparation. In other cases, it may be delayed and appear after one or several applications. No immunological phenomena are involved in this type of direct irritancy. The susceptibility to this type of response is difficult to detect beforehand. Patch and other tests on the skin employed by dermatologists and allergists may give no clue that this type of reaction will occur (Refs. 6 and 11).

8. *Local sensitivity.* In addition to "irritancy," ingredients in oral health care products produce a type of sensitization involving immunological phenomena. The manifestations of such sensitization may be local or systemic. Topical sensitization may result from prolonged or repeated contact of an ingredient with the mucous membranes of the mouth and throat (Refs. 12 and 13). Under these circumstances, an ingredient may serve as a contact allergen by acting as a hapten becoming bound to the protein in the cells of the mucous membranes or submucosal structures. Stimulation of the T cell division of the lymphoid system occurs. Lymphoid cells become sensitive to the contact allergen or the hapten and accumulate in the mucosa, the submucosal layers, or even in the skin. The drug may pass through the mucous membranes, circulate in the blood, combine with proteins in the skin, and not sensitize the mucous membranes. Contact of the sensitized lymphocytes with the ingredient at a later date provokes a cell-mediated sensitivity type of reaction characterized by inflammation, burning, erythematous ulcerations, or exudation at the site of application. This type of response is cytotoxic, since it affects lymphocytes and no immune bodies are involved (Refs. 13 and 14). Topical sensitization of this type may, at times, be difficult to distinguish from direct topical "irritancy." The resulting contact sensitivity in a particular individual manifests immunological specificity for the particular ingredient (hapten). Patch-testing may be helpful in detecting this type of sensitization when the skin has been sensitized. However, since the proteins of the skin differ from those of the mucous membranes and the hapten may not have passed into the skin a negative patch skin test may be misleading because sensitization may have occurred in the mouth and throat even though the skin has not become sensitized. Contact of the agent with the mucous membranes would produce a reaction. Coombs and Gell (Ref. 13) have classified immune responses into four distinct types. They designate this type of response as Type IV (cytotoxic). It has also been called "delayed hypersensitivity." The allergen or the hapten interacts with the sensitized lymphocytes in the mucous membranes, or submucosal tissues. The lymphocytes disintegrate and produce tissue damage (Ref. 15).

9. *Systemic sensitization.* A hapten may be inhaled, injected, taken orally, come in contact with a mucous membrane of the mouth or throat, trachea, lungs, and other organ sites, or pass through damaged skin and bind with proteins in blood and other tissue fluids to produce a systemic type of sensitization. This was once referred to as the "humoral type" or immediate type of sensitization. This type of sensitization is due to circulating IgE of the blood protein fraction. Coombs and Gell (Ref. 13) designate this type of response as the Type I response. It occurs in the allergic-prone (atopic) individual and is associated with a hereditary tendency towards sensitization. Allergens (also called antigens) are usually proteins or lipoproteins of high molecular weight. Drugs of low molecular weight, often referred to as haptens, combine with proteins and act as allergens that cause a systemic type of sensitization by

stimulating the production of circulating antibodies (immune bodies) of the IgE class of globulins (Refs. 16 and 17).

Antibodies are found in the globulin fraction of blood proteins. Ordinarily, immune bodies are protective and neutralize an antigen, allergen, or a hapten on contact by forming an antigen-antibody complex which is harmless to the organism and prevents a reaction. In susceptible individuals, for unknown reasons, the antibody acts in an adverse (pathologic) manner and sensitizes certain cells in the body, referred to as target cells. IgE antibodies have a cytophilic affinity for the membranes of mast cells, blood neutrophils, and basophils in susceptible individuals (Ref. 13). These antibody-sensitized cells rupture on subsequent contact with the appropriate allergen or hapten (drug) and release vasoactive substances that dilate or constrict blood vessels. At least one or more exposures and an incubation period of at least a week are necessary for immune bodies and this type of sensitization to develop. The B cell division of the lymphoid system is involved in the systemic type of immune response (Ref. 13). It is due to circulating antigens. The presence of antibodies that sensitize cells is necessary for sensitivity reactions to occur. This type of sensitization may be manifested by anaphylaxis, extrinsic asthma (systemic), rhinitis (systemic), subcutaneous edema, laryngeal and pharyngeal edema (systemic), urticaria, or atopic dermatitis (Refs. 14 and 16).

Antigens have certain groups of amino acid complexes on their structure which determine the specificity of the antigen and the type of antibody that forms. These chemical sites are called antigenic determinants. The antibody has certain receptor sites on its molecule into which the antigen determinant fits in a lock-and-key manner to form the antigen-antibody complex. Each antigen has its own number of natural groups of antigenic determinants. When a drug acts as a hapten, an additional antigenic determinant not ordinarily found on the antigen is added to the protein. In the production of the antibody, a receptor forms on the antibody that accepts the hapten-protein antigen or the hapten itself (Ref. 17).

Drugs that are in the same chemical family may produce cross-sensitization or may cross-react in susceptible individuals if the antigenic determinant or hapten can fit into the same receptor of an antibody. However, even a slight modification of the chemical structure between two closely chemically allied drugs may negate this type of reaction. Aminobenzoic acid, for example, is closely allied chemically to its ester, ethyl aminobenzoic acid (benzocaine). Yet, it does not necessarily follow that both of these compounds, even if they bind on the same antigenic determinant of a protein, will cause cross-sensitization unless they fit into the same receptors on the antibody (Ref. 13). The Panel finds that the incidence of cross-sensitization of drugs used in oral health care preparations is low and does not consider this to be a serious problem.

Human IgE antibodies will also bind to the plasma membranes of mast cells in the skin and mucous membranes and cause sensitivity reactions when the appropriate antigen (or hapten) circulates in the blood or comes into contact with these cells following oral ingestion, parenteral injection or percutaneous absorption. The response may be local or generalized and even may be cutaneous (Refs. 9, 16, and 17).

The systemic type of sensitization differs from the topical sensitization which is due to a contact allergen. A topical sensitization causes a cell-mediated type of reaction. A systemic type of sensitization elicits an adverse response to an antigen-antibody complex acting on sensitized target cells (Ref. 13). The anaphylactic type of reaction is the most serious. It may occur suddenly, with little or no warning, and may be fatal. A trace of the offending ingredient coming into contact with the mucous membranes or administered orally or parenterally to a sensitized person may precipitate the sudden release of mediators, such as massive quantities of histamine, serotonin, slow-reacting substance (SRS–A), the eosinophilic chemotaxic factor or various kinins. These mediators, acting on the blood vessels, cause them to dilate and may cause syncope, shock, and death in a matter of minutes. These substances are released from the mast cells and white blood cells, particularly basophils and neutrophils. Fortunately, this type of reaction is rare.

Marketing experience of oral health care products indicates that the frequency of anaphylaxis from topical application on the mucous membranes has been infrequent. A drug itself may act directly, in the absence of immune bodies, on mast and other cells and cause histamine or other mediator release. This type of reaction is often called anaphylactoid. It resembles anaphylaxis except that the causative mechanism is different (Ref. 13).

Fortunately, this type of reaction also is uncommon. Testing for sensitivity, particularly for anaphylaxis in allergic patients, may be dangerous because the quantity used for testing may be fatal in susceptible individuals. An anaphylactic or anaphylactoid reaction may occur the first time a drug is applied topically to a mucous membrane or to the skin. The anaphylactic and anaphylactoid types of reactions may be delayed, but the manifestations, when fully developed, are similar to the immediate-occurring type (Ref. 16 and 17).

Other manifestations of systemic sensitization that may occur are relatively benign and disappear with proper treatment or discontinuing use of the drug. Among these manifestations are rhinitis, asthmatic attack, urticaria (hives), and atopic dermatitis. Generally, histamine is the most common offender in causing these responses, but other mediators may also be responsible (Ref. 18).

All soluble drugs can act as haptens and cause sensitization. Antihistamines, despite the fact that they are used systemically for treating allergies, can act as haptens and be sensitizers when applied topically. The "caine" types of local anesthetics and modifications of the "caine" type cause sensitization to a greater extent than the alcohol type of ingredients although the alcohols may also produce irritancy and sensitization. The quaternary nitrogenous derivatives can also act as haptens and be sensitizers when applied topically. Similarly, phenolic-type compounds and pharmaceutical necessities such as flavorants can act as haptens (Refs. 16 and 19).

People who are allergic to foods, inhalants, and other substances are high risks and are more apt to become sensitized to drugs (Ref. 10).

Data are meager on the frequency of sensitization by ingredients used in oral health care products and on the relationship of occurrences in a target population. The Panel believes that the long-term usage and marketing experience, over many years, of the majority of these ingredients justifies their continued use and that the hazards due to sensitization are minimal. The labeling of oral health care products must indicate that a product should not be used if a subject is known to be sensitive to any of the ingredients used in its formulation. The Panel recommends the following general warning in the labeling of all active ingredients in oral health care products: "Discontinue use and consult a physician if irritation persists or increases or a rash appears on the skin."

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 30, 1957.

(2) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, p. 55, 1976.

(3) Knoefel, P. K., et al., "Absorption, Distribution, Transformation and Excretion of Drugs," Charles C. Thomas, Springfield, IL, pp. 49–55, 1972.

(4) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 46–47, 1976.

(5) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Texbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 26–36 and 55–56, 1965.

(6) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 26–36, 1965.

(7) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 100–102, 1976.

(8) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 55–56, 1965.

(9) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Texbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 33–34, 1965.

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

(11) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Phildelphia, pp. 36–68, 1976.

(12) Heisel, E. B., "The Skin: Basic Consideration," *in* "Dermatologic Allergy," edited by J. H. Criep, W. B. Saunders Co., Philadelphia, pp. 3–9 1967.

(13) Coombs, R. R. A., and P. G. H. Gell, "Classification of Allergic Reactions Responsible for Clinical Hypersensitivity and Disease," *in* "Clinical Aspects of Immunology," 2d Ed., edited by P. G. H. Gell and R. R. A. Coombs, F. A. Davis Co., Philadelphia, pp. 575–596, 1968.

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

(15) Wells, J. V., "Immune Mechanisms in Tissue Damage," *in* "Basic and Clinical Immunology," 2d Ed., edited by H. H. Fudenberg et al., Lange Medical Publications, Los Altos, CA pp. 278–281, 1978.

(16) Frick, O. L., "Immediate Hypersensitivity," *in* "Basic and Clinical Immunology," 2d Ed., edited by H. H. Fudenberg et al., Lange Medical Publications, Los Altos, CA, pp. 246–266, 1978.

(17) Harper, H. A., V. W. Rodwell, and P. A. Mayes, "Review of Physiological Chemistry," 16th Ed., Lange Medical Publications, Los Altos, CA, pp. 596–608, 1977.

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

(19) Jawetz, E., J. L. Melnick, and E. A. Adelberg, "Review of Medical Microbiology," 12th Ed., Lange Medical Publications, Los Altos, CA, pp. 143–168, 1976.

F. Principles Applicable to Combination Products

1. *General comments.* In reviewing OTC oral health care preparations for use on the mucous membranes of the mouth and throat, the Panel was mindful of the OTC review regulations (21 CFR 330.10(a)(4)(iv)) which state:

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

The Panel concurs with the basic concepts embodied in this regulation that each active ingredient in a combination product must contribute to the claimed effects and that the combination must provide rational concurrent therapy. The Panel believes that it is irrational to use a combination product unless each active ingredient contributes to the effective treatment of at least one of the labeled symptoms for which the combination of ingredients is recommended.

The Panel has outlined below the proposed standards for combinations for all the ingredients reviewed. Also included are elaborations and reasons for the rationality or irrationality of combining the various ingredients with each other and other Category I ingredients considered by other panels.

It is accepted medical practice to use only drugs that are necessary to safely and effectively treat a patient. Only single-ingredient products are used to treat a particular symptom or disease entity in most cases. The Panel believes strongly that this concept should apply to self-medication as well since the consumer is treating symptoms without the advice of a physician. OTC products containing effective single active ingredients are, therefore, preferred to those having multiple active ingredients. Products containing a single active ingredient reduce the possibility of the occurrence of toxic, allergic, and idiosyncratic reactions, and possible unrecognized and undesirable drug ineractions. This is the case when a drug is prescribed by a physician and should also be the case when a drug is used by a layman for self-treatment. It is the opinion of the Panel that in general OTC oral health care preparations should contain only one Cateogry I active ingredient of a pharmacologic class and such inactive ingredients as are necessary for pharmaceutical formulation.

The Panel recognizes that select situations may exist in which combinations of ingredients from the same pharmacologic class of Category I active ingredients or from different pharmacologic classes but exerting similar therapeutic effects may be used to treat the same symptoms or conditions. The Panel does not wish to deprive the consumer of the right to use these products if they possess a therapeutic advantage not possessed by each of the individual ingredients used alone. By "therapeutic advantage" is meant that the product provides either enhanced effectiveness, safety, consumer acceptance, or improved quality or formulation. Category I active ingredients of the same therapeutic category may be combined if each active ingredient is present in full therapeutic doses or in subtherapeutic doses where a subtherapeutic dose is appropriate. The combination product must meet the OTC drug combination policy as cited above (21 CFR 330.10(a)(4)(iv)) in all respects and must be equal to or superior to each of the active ingredients used alone at full therapeutic doses when considered from the standpoint on a benefit-to-risk ratio. When it is not known or it has not been shown and data have not been presented that the foregoing conditions exist, the combination should not be placed in Category I.

An ingredient claimed to be a pharmacologic adjuvant will be considered an active ingredient and may be included in addition to one or more principal active ingredients only if it meets the combintion policy in all respects.

When there are data available indicating that a particular ingredient in a given combination is appropriate for use only in that combination, but is not in Category I as a single active ingredient, such an ingredient will be placed in Category I for use only when used in that particular combination.

Many combinations of oral health care products intended to be used in the mouth and throat have been in the marketplace for many years. Many of

these products continue to be used for self-medication for various clinical conditions and symptoms, even though use for these conditions has been supplanted, for the most part, by other more effective or safer drugs and methods of treatment. The Panel feels that both the OTC drug review regulations (21 CFR Part 330) and the historical evidence for the use of these combination products do not support the concept that the long-time use of an OTC product with apparent beneficial results based on impressions by consumers or without complaints of adverse reactions attest to their safety and effectiveness. The Panel is not impressed by statements appearing in some submissions, such as "marketing experience has been favorable" or "no complaints have been reported." The Panel considers marketing experience data and frequency of customer complaints to be of interest and gives them their due consideration but does not consider such data to be the type of proof that is meaningful in a scientific review of standards for existing OTC products. The paucity or lack of reports of adverse reactions are merely negative findings and are not indications or evidence of the fact that adverse reactions have not occurred. Negative findings from marketing data do not constitute a sound basis for establishing the safety and effectiveness of a product. Furthermore, most of the submissions do not describe the manner in which the data were collected from the users of these products or the instructions provided the users to facilitate and assure that all necessary meaningful data would be forthcoming in reporting adverse reactions. Very few of the submissions describe how and by whom the data were collected and interpreted or otherwise explain pertinent significant details concerning their methods of adverse reaction reporting.

The Panel, therefore, does not feel that the continued availability and use of a combination product is justified simply because such combinations have had an extensive, apparently successful marketing history.

The Panel is aware of the lack of controlled studies in the area of certain combinations used in the mouth and throat. Most studies of these types of products are of necessity of a subjective nature. Controlled clinical studies are difficult to perform, particularly for symptoms which are frequently evanescent and usually self-limited. The Panel is also aware that it is not always possible to interest investigators in such studies. The Panel agrees with FDA's conclusions of concerning difficulties in performing controlled clinical studies to determine the safety and effectiveness of these products which were published in the **Federal Register** on November 12, 1973 (38 FR 31261):

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

2. *Requirement of contribution.* The Panel has determined that each claimed active ingredient in a combination must make a contribution to the claimed therapeutic effect. The amount of ingredient present in a product intended for use in the oral cavity must be at least equal to the currently accepted minimum dose level for such active ingredients as required in the ingredient statements below unless data are presented to show that a lower minimum dose is adequate to achieve the intended therapeutic effect.

In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all the combinations submitted. All combinations that meet the criteria for Category I as set forth below are considered safe and effective.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product. Where lacking, data should be developed by appropriate, well-controlled clinical studies to demonstrate the effectiveness of a dosage level.

Each claimed active ingredient in an oral health care combination product must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient having a claimed local effect on the oral and pharyngeal mucous membranes that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient and is not generally recognized as safe and effective. Appropriate animal and human testing and prior approval by FDA is required before a product containing such an ingredient may be marketed.

The Panel considered only those combination products submitted pursuant to the notice published on July 20, 1973 in the **Federal Register** (39 FR 19444). The Panel recognizes that other combination products may be in the marketplace, but it has either no knowledge of such products or insufficient data with respect to such products to make a reasonable judgment of safety or effectiveness. Accordingly, the Panel recommends that any new combination or any presently marketed combination which claims local effects on the oral and pharyngeal mucous membranes and not submitted to this Panel could be evaluated through the new drug procedures or be the subject of an appropriate petition to FDA to review or amend the OTC oral cavity drug monograph.

3. *Standards for determining Category I Combinations*—a. *Combinations of ingredients from different therapeutic categories.* Combinations of ingredients from different therapeutic categories must be limited to Category I oral health care ingredients in the dosage range specified for Category I ingredients in the ingredient satements. The following combinations are classified as Category I:

(1) One Category I topical anesthetic/analgesic may be combined with one Category I antimicrobial active ingredient. The topical anesthetic/analgesic relieves pain while the antimicrobial active ingredient is acting on the oral microorganisms. The majority of antimicrobial ingredients reviewed by the Panel are not anesthetic/analgesic ingredients and do not relieve pain.

(2) One Category I demulcent active ingredient may be combined with one Category I antimicrobial active ingrdient. The demulcent provides a soothing effect while the antimicrobial agent is acting on the oral microoganisms.

(3) One Category I decongestant active ingredient may be combined with one Category I antimicrobial active ingredient. This combination is rational because the decongestant may help reduce the edema while the antimicrobial agent is acting on the oral microorganisms.

(4) One Category I astringent may be combined with one Category I antimicrobial active ingredient because astringents provide a protective coat on ulcerated areas and aid in relieving discomfort while the antimicrobial agent is acting on the oral microorganisms.

(5) One Category I anesthetic/analgesic active ingredient may be combined with one Category I demulcent active ingredient. The anesthetic/analgesic relieves pain and the demulcent may augment this effect

by acting as a protectant and minimizing effects of external stimuli.

(6) One Category I anesthetic/analgesic active ingredient may be combined with one Category I decongestant active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receiptors, and the decongestant reduces swelling that may be stimulating pain receptors.

(7) One Category I anesthetic/analgesic active ingredient may be combined with one Category I demulcent active ingredient and with one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by supressing the pain receptors. The demulcent reduces the degree of stimulation of the pain receiptor on a surface lesion, while the antimicrobial ingredient is acting on the oral microorganisms.

(8) One Category I anesthetic/analgesic active ingredient may be combined with one Category I Astringent active ingredient. The anesthetic/analgesic relieves pain by supressing the pain receptors, and the astringent acts as a coagulant and provides a protective coating for a surface lesion, theregy reducing the number of stimuli affecting that area.

(9) One Category I anesthetic/analgesic active ingredient may be combined with one Category I astringent active ingredient and the one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receptors, and the astringent acts as a coagulant providing a protective coating for a surface lesion, thereby reducing the number of stimuli affecting that area. The antimicrobial agent acts on the oral microorganisms.

(10) One Category I anesthetic/analgesic active ingredient may be combined with one Category I decongestant active ingredient and with one Category I antimicrobial active ingredient. The anesthetic/analgesic relieves pain by suppressing the pain receptors. The decongestant helps reduce the edema, and the antimicrobial agent acts on the oral microorganisms.

b. *Combinations of ingredients from the same therapeutic category.* Category I active ingredients of the same therapeutic category but having different pharmacologic mechanisms of action and those that have the same action may be combined if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate, but only where there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

4. *Standards for determining Category II combination products.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and effective, if any of the following apply:

a. The combination contains any Category II ingredients or any ingredient is present above the maximum dose range for that ingredient allowed in the ingredient statement in this document.

b. One or more antimicrobial active ingredients are combined with one or more expectorant active ingredients, because the expectorant would dilute or diminish the time of contact of the antimicrobial drug with the diseased surface.

c. One or more antimicrobial ingredients are combined with any debriding active ingredients because a debriding agent would dilute or wash away the agent from the diseased surface.

d. One or more antimicrobial active ingredients are combined with an expectorant and one debriding agent because the duration of contact would be decreased or the drug washed away from the mucous surface.

e. One or more anesthetic active ingredients are combined with one debriding active ingredient because the anesthetic would be washed away, diluted, or mixed with the debris.

f. One or more anesthetic active ingredients are combined with one or more expectorants because the drug would be diluted and removed from the site of action.

g. One or more anesthetic active ingredients are combined with one or more expectorants, combined with one or more debriding agents because the anesthetic agent would be diluted or removed from the diseased site.

h. One or more active astringents are combined with one or more debriding agents because the debriding agent would prevent the astringents from exerting its coagulating effect.

i. One of more active astringents are combined with one or more expectorants because the expectorant would dilute and wash away the astringent and prevent it from acting as a coagulant.

j. One or more active astringents are combined with one or more expectorants and one or more debriding agents because the astringent would be diluted or washed away or otherwise be prevented from exerting its coagulating effect.

k. One or more decongestants are combined with one or more expectorants because the expectorant would dilute or otherwise prevent the decongestant from exerting its therapeutic effect.

l. One or more decongestants are combined with one or more expectorants, combined with one or more debriding agents because the debriding agent and the expectorant would dilute or wash away the decongestant or otherwise prevent it from exerting its therapeutic effect.

5. *Standards for determining Category III combinations.* A combination is classified as a Category III combination if any of the following apply:

a. Any Category I ingredient is below the minimum effective dose set by the Panel as found elsewhere in this document for such respective ingredient, except that Category I active ingredients of the same therapeutic category but having different pharmacologic mechanisms of action, and those that have the same action, may be combined if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate but only where there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

b. One or more ingredients are Category III ingredients, as set forth elsewhere in this document for single active oral health care product ingredients.

c. A combination of two or more Category I active ingredients from the same pharmacologic class or from different pharmacologic classes but exerting similar therapeutic effects has not been shown to possess a therapeutic advantage, i.e., enhanced effectiveness, safety, consumer acceptance, or improved quality of formulation greater than each active ingredient used alone at full therapeutic doses.

6. *Requirements for the reclassification of Category III combinations to Category I combinations*—a. *Combinations with ingredients below minimum effective levels.* For any Category III combination where one or more ingredients fall below the minimum effective level as set forth elsewhere in this document for such individual ingredients, tests must be performed to substantiate the effectiveness of any such ingredient. The Panel recommends a petition to the agency for appropriate modification of the monograph to permit such lower dosages, or that testing be pursued under the NDA procedures.

b. *Combinations containing Category III ingredients.* Any combination that contains one or more ingredients in Category III, as set forth elsewhere in this document, must be tested to satisfy

Category I requirements for each such ingredient.

7: *Inactive ingredients.* The Panel recommends that a review panel be appointed to review the inactive ingredients in OTC products for the purpose of determining which of these inactive ingredients should be listed on the label.

III. Anesthetics/Analgesics

A. General Discussion.

1. *Modes of action.* Topical anesthetics/analgesics act in one or a combination of the following ways:

a. They may penetrate the epithelial barriers of the mucous membranes and completely block the receptors for the perception of pain. Such ingredients penetrate the nerve endings and cause a temporary reversible change in the nerve membrane that prevents the development of the electrical current that transmits sensory impulses along a nerve. When this occurs, a complete loss of perception of stimuli such as pinprick, touch, warmth, cold, and pressure results. When the blockade is complete, the anesthetics may induce the subjective sensation of numbness. This lack of sensation and response to pain is called anesthesia (without feeling) (Ref. 1).

b. Topical anesthetics/analgesics may act by partially blocking the transmission of impulses from the receptors for pain so that subminimal stimuli that elicit the sensation are no longer able to do so. However, the receptors are still able to respond to stronger stimuli that induce pain. This type of response is noted after application of these ingredients in dilute form so that the smaller C-type pain-carrying fibers are blocked but the larger A-type fibers are not. Ingredients acting in this manner generally do not induce the sensation of numbness. The sensations of cold, warmth, touch, or pressure usually remain undisturbed. For this reason, such ingredients are called analgesics. In this report the term "anesthetic/analgesic" is used. It should be emphasized that anesthetics in smaller doses will act as analgesics and not produce numbness. An analgesic, on the other hand, will not produce anesthesia when the dosage is increased, but might produce toxic reactions.

c. Some topical anesthetics/analgesics may penetrate the mucous membranes and exert an anti-inflammatory effect when they come into contact with a disease process that is causing discomfort in the mucous membranes. Such ingredients do not act upon receptors and nerve fibers to block transmission of impulses. They may reduce swelling in tissues by acting as antagonists to agents causing inflammation, thereby eliminating noxious stimuli that cause pain. Relief from the discomfort will require time because the anti-inflammatory effects occur gradually and are not immediately apparent. The salicylates exert anti-inflammatory effects when ingested orally. Other salicyclates and other mild anesthetics/analgesics such as antipyrine do not cause a blockade in nerve tissues.

d. Topical anesthetics/analgesics may act antagonistically to biologic agents stored in certain cells in the body. When released into the tissues by trauma or some pathologic mechanism, these agents cause cellular injury. Histamine, serotonin, various kinins, prostaglandins, etc., are stored in mast cells or white blood cells. When released into tissues where they are not ordinarily found, they exert a vasoactive effect and produce an inflammatory swelling of the cells or another not clearly understood response that results in discomfort and pain. The histamine response is characterized by swelling of the tissues, engorgement of blood vessels, and escape of fluid from the blood vessels into tissue spaces. Topical anesthetic/analgesic ingredients that antagonize the effects of histamine are called antihistamines.

e. Topical anesthetic/analgesic ingredients provide temporary symptomatic relief and are not curative. Salicylates and antihistamines may ameliorate a disease process. Relief of symptoms beyond the time the medicine exerts its topical anesthetic/analgesic effect sometimes occurs from the use of agents that directly or indirectly decrease or overcome muscle spasm, reduce edema, or alter the degree of blood flow in an affected area. Exactly how this comes about is not known.

Topical anesthetics/analgesics are applied to the mucous membranes to lessen or completely abolish pain. They act by completely blocking pain receptors resulting in a sensation of numbness and abolition of responses to painful stimuli. In some instances, not all the pain fibers are completely blocked. The smaller, unmyelinated (unsheathed) C fibers that carry the sensation of dull, aching pain are more easily blocked than the large delta A myelinated (sheathed) fibers which carry the sensation of sharp pain. Only a partial reduction in the response to painful stimuli results, but it is sufficient to alleviate discomfort of the dull, aching type of pain if the C fibers are blocked. This partial relief is rightfully called "analgesia." If all the fibers in a nerve are blocked, and no response occurs to painful stimuli, the sensation of numbness results. This is rightfully called "anesthesia." In this report, the active ingredients which produce either analgesia or anesthesia are called "anesthetics/analgesics."

2. *Chemical classification of anesthetics.* Topical anesthetics used in the mouth and throat fall into two chemical groups. One group is the nitrogen-containing amino type of anesthetics, and the other group is the hydroxy or alcohol type (Ref. 2).

The nitrogenous types are closely allied to ammonia, since the hydrogen atoms of ammonia are substituted by organic radicals. They form weak bases when dissolved in water and, like ammonium hydroxide which forms when ammonia is dissolved in water, are poorly ionized.

The solubility of the bases of nitrogenous anesthetics in water varies. Aqueous solutions of amines are alkaline. These basic compounds form salts when combined with acids just as ammonium hydroxide does when it is mixed with an acid to form a salt. The salts formed when amines combined with acids are far more soluble in water than the bases. They are also more stable. The un-ionized base is the physiologically active form of the compound.

Exactly how these ingredients exert their physiological effect is not known, but it is believed that they change the pore size on the axonal membrane and distort the channels for passage of the sodium ion from the extracellular fluid around an axon (the core of the nerve fiber) and prevent depolarization of the axonal membrane. This process has been referred to as stabilization of the membrane. The electrical impulse generated proximally at an unaffected part of a nerve cannot pass the affected area. The action of topical anesthetics is reversible and no permanent change results in the membrane. Salts of topical anesthetics are ineffective in producing a blockade because they are highly ionized and do not penetrate lipid membranes easily. However, when they are injected into tissues perineurally or applied on the mucous membranes, they are converted to the basic form because of the buffering action of the tissues. The salts, therefore, are effective topically on mucous membranes unless an excess is used. If an excess is applied, enough acid is liberated to neutralize the bases in the buffers, nullifying their effects.

The nitrogen-containing topical anesthetics are subdivided into several chemical types. These are described in more detail below. A particular

chemical configuration appears in the majority of the nitrogenous type of topical anesthetics. This configuration is composed of a hydrocarbon nucleus (benzene ring) and a nitrogen atom in the form of a tertiary amine, between which is interposed an intervening two-carbon chain, often called the pivot. These amines are the most potent, effective, and serviceable topical anesthetics. They are also the most toxic systemically if they gain access to the bloodstream. The most effective and potent drugs have an ester or amide group linking the pivot to the hydrocarbon nucleus. Benzocaine, butamben, cocaine, and tetracaine are esters. Benzocaine is the most widely used type of ester in OTC products. The amide type of this topical anesthetic consists of a benzene ring linked to the two-carbon chain by an amide group. The end of the two-carbon chain also carries the tertiary amino group, as is the case with the ester type. Lidocaine and dibucaine are other amides that have been proposed for OTC use in the oral cavity.

The nitrogenous topical anesthetics are polar substances. The benzene ring, often called the aromatic portion, is called the lipophilic pole since it is oriented toward lipid (fatty) materials in nerve cells or the axon since nerve tissues are, relatively speaking, rich in fatty materials. The water-soluble or hydrophilic amino pole is directly opposite to the aromatic pole separated by the carbon chain. This amino pole becomes oriented into the watery phase of a medium, a cell, or cell membrane. Thus, to be effective, topical anesthetics should be sufficiently lipid soluble to penetrate lipid barriers and sufficiently water soluble to be transported to the cell

The generic names of most topical anesthetics end with the suffix "caine." The "caine" type of compounds are subdivided into two types, the water-soluble (tetracaine, lidocaine) type and the "insoluble" derivatives (benzocaine, orthoform, butamben). The so-called "insoluble" anesthetics are poorly soluble in water but are lipid soluble. However, they are not totally insoluble or they would not be effective since they would not be transmitted to the cells (Refs. 2 and 3). Because of their low degree of water solubility, they have low systemic toxicity since they are not readily absorbed and do not readily pass into the blood to accumulate to toxic levels. The highly water-soluble compounds are readily absorbed from the mucous membranes. When applied in excessive quantities, they may be absorbed so rapidly that toxic plasma levels result that can cause life-threatening or even fatal reactions. The systemic effects of these topical anesthetics are unwanted. The topical effect is the desirable effect. As long as these drugs remain in the area of the nerve endings and nerve trunks and pass slowly from the tissue fluids into the bloodstream, the amount circulating in the blood is insignificant and causes no systemic reaction (Ref. 4). In some cases the amount of drug that produces diminished sensation systemically is 500 or 600 times greater than an effective topical dose. An amount of drug which is 500 or 600 times greater than that which is effective topically can be fatal. Systemic reactions are characterized initially by stimulation of the nervous system and are manifested by convulsions. The convulsions are due to depression of the inhibitory neurons in the motor cortex. The excitatory neurons remain active. If the plasma concentration is increased still more, the excitatory neurons, in turn, are depressed. The reaction that follows is cerebral depression characterized by coma, paralysis, and cessation of respiration.

In addition, "caine" type anesthetics also depress the cardiovascular system, acting on both the heart and blood vessels. They depress conduction in the heart and disturb its rhythm and also reduce cardiac output. In addition, "caine" type anesthetics relax the blood vessels resulting in a decrease in blood pressure. The effects on the heart can occur simultaneously with the effects on the central nervous system. The systemic reactions, therefore, are of two types and are referred to as the "central nervous system type" and the "cardiovascular type." Generally, the central nervous system type of reaction is the more prominent and occurs first. These two types of systemic reactions occur from time to time following the use of these ingredients as prescription products.

The Panel considers the majority of these topical anesthetic/analgesic ingredients as unsafe for OTC use and has classified most of them as Category II. Benzocaine, however, due to its low water solubility and barely detectable blood level, does not cause systemic reactions. For this reason, it is one of the safest, least toxic, and most effective of the "caine" type anesthetics (Refs. 5 and 6).

Of all the nitrogen-containing topical anesthetics used in OTC products, many are of the "caine" type; however, there are nitrogen-containing topical anesthetics used in OTC products which are not of the "caine" type. Some have structures that are modifications of this classical chemical configuration characteristic of the "caine" class of drugs (Ref. 2). The aromatic nucleus may be attached to the remainder of the molecule by a ketone, ether, or other type of linkage instead of the ester and amide type (Ref. 2). The two-carbon chain may have side chains. The names of these types of derivatives usually bear the suffix "-ine" instead of "-caine." Pramoxine and dyclonine are nitrogen-containing compounds that are examples of non-"caine" type drugs. Their molecules are modified sufficiently so that they are effective as topical anesthetics; if they are absorbed, they may produce systemic responses but not of the severity of those which are characteristic of the "caines." These non-"caine" anesthetics are irritating and may cause sloughing. They are not effective when injected perineurally, but are effective when applied topically on the mucous membranes. Therefore, they are used topically, but are not suitable for injection. They do not cause convulsions, but some non-"caine" anesthetics may cause cardiac depression.

Some antihistamines have structures that are modifications of the "caine" type of topical anesthetics. They possess, in addition to the antihistamine effect, a topical anesthetic effect as well (Refs. 1 and 2). Their names bear the suffix "-ine" also. Some antihistamines are suitable topically for anesthesia, but not for injection (Ref. 2). These are described below.

The second type of topical anesthetic mentioned above, the alcohol or hydroxy type, consists of non-nitrogenous compounds. The alcohol-type drugs, such as phenol, benzyl alcohol, hexylresorcinol, and salicyl alcohol do not cause central nervous system or cardiovascular effects characteristic of the "caine" type drugs. The alcohols may be cyclic, aliphatic, or aromatic. Some of the drugs in the volatile oil group, such as menthol, camphor, and other cyclic alcohols, have topical anesthetic action. Systemic effects, if they occur, vary with the individual compound. Alcohol-type anesthetics are effective when applied topically, but produce neurolysis when injected perineurally. The hydroxy compounds are polar substances and are believed to orient into the cell membrane in the same manner as the nitrogen-containing compounds. They possess varying degrees of lipid solubility. Their action does not depend upon pH as is the case with the nitrogen-containing compounds. They

are readily absorbed through the mucous membranes and intact skin.

The "water-insoluble" esters, such as benzocaine and butamben, which are considered to be "caine" type drugs, are not absorbed in sufficient quantities to produce plasma levels that cause systemic reactions and, therefore, are relatively safe. Convulsions and cardiac depression do not occur from the use of these types of compounds. These have been used as anesthetics in oral health care products without any serious toxic effects. They are effective on the mucous membranes, the poor water solubility notwithstanding. They are soluble in glycols and other similar water-soluble bases and are readily applied in effective concentrations, in the form of rinses or sprays, to the mucous membranes of the mouth and throat. Bioactive quantities are delivered to paid receptors when solutions prepared with these solvents are applied to a surface. The degree of anesthesia that results depends upon the quantity used.

Topical anesthetics readily traverse the epithelial barriers of the mucous membranes and pass into the tissue fluids beneath, into the venules and lymphatics and are then distributed to various tissues, particularly those that are capillary-rich. Some esters of para-aminobenzoic acid, such as tetracaine and benzocaine, are hydrolyzed by plasma esterases into the alcohol and acid from which they were formed and thereby inactivated. The portions that are not metabolized in the blood are inactivated by the liver. The amide type of topical anesthetic is not hydrolyzed by esterases, but ultimately passes from the blood and tissues to the liver when it undergoes biodegradation (detoxification) through various metabolic pathways, such as oxidation, reduction, etc. The byproducts are eliminated in the urine.

Topical anesthetics, such as dibucaine and cocaine, that are not hydrolyzed by plasma esterases are not detoxified by the liver and are eliminated unchanged by the kidney. The alcohol type of topical anesthetic is not affected by the plasma esterases. Such anesthetics are detoxified by the liver by various types of chemical reactions, such as oxidation, reduction, hydrolysis, conjugation, or transfer reactions. Unmetabolized portions are excreted in the urine. Solvents and other substances used to formulate a finished product that penetrates the epithelial barriers are detoxified in the same manner as the active ingredients. It is possible for highly lipophilic substances that are used daily, for long periods of time, particularly if they are not readily biodegradable, to accumulate in the adipose and other lipid-rich tissues where they remain for days, weeks, or months depending upon their half-lives in the body. None of the ingredients the Panel has evaluated are retained for long periods of time in adipose or lipid-rich tissues.

Antihistamines and other topical anesthetic drugs not fitting into the "caine" type or derivatives related to the "caine" categories described above are absorbed, distributed, metabolized, and excreted in the same manner as those described above. In many cases, the exact metabolic fate is not known. Antihistamines are discussed in detail below. (See part III. paragraph A.3. below—Antihistamines used as anesthetics in the oral cavity.)

When two of the "caine" type of topical anesthetics are combined, they act additively as far as systemic toxicity is concerned. Adriani and Zepernick (Ref. 7) showed that if half of a dose of lidocaine that causes central nervous system excitation manifested by seizures is combined with half of the dose of tetracaine that does the same, intravenously in a dog, the two act additively and cause seizures. They also showed that when equal volumes of aqueous solutions of lidocaine and tetracaine in concentrations that produce the maximal topical effect on the mucous membranes beyond which no further benefit is gained by increasing the concentrations are combined, the duration of action of the combination is that of the longer-lasting drug (Ref. 7). Combining the two drugs does not increase the duration of anesthesia. The latent period, i.e., the time interval between the moment of application of the drug and the moment the anesthesia is perceived, is the same as that of the shorter-acting drug.

These topical anesthetics can produce a complete blockade and anesthesia that abolish reflex activity in the pharynx and larynx. This degree of blockade is necessary for completion of endoscopic or other surgical procedures. The drug does not penetrate beyond the mucous membranes; therefore, surgery of deeper structures cannot be performed by using topical anesthesia. In the treatment of painful disorders of the mouth, this degree of blockade is not required and is undesirable since there is a possibility that loss of gag and laryngeal reflexes might lead to aspiration of secretions, food, and other foreign substances. Aspiration under these circumstances is more of a possibility in subjects who have difficulty in swallowing due to neurological diseases, muscle dystrophies, or in elderly subjects in whom the gag reflexes are decreased in activity. Doty and Bosma (Ref. 8) have shown that application of cocaine or lidocaine respectively does not alter the swallowing reflex. With drugs such as benzocaine and benzyl alcohol, the minimum effective anesthetic concentration is advocated. Only a partial blockade is sought and induced. These drugs are administered in the oral cavity in the form of lozenges which are slowly dissolved in the mouth so that a continuous bathing of the mucous membranes occurs. The quantity released from the lozenge should be sufficient to alleviate discomfort, but it should not be so great as to produce a complete loss of reflexes and numbness.

The salicylates and chemically and pharmacologically related "analgesics," such as aspirin and antipyrine, have been advocated for use topically to relieve painful conditions in the mouth and throat. Neither the salicylates nor other analgesics block the neuronal membranes as do the topical anesthetics.

3. *Antihistamines used as anesthetics/analgesics in the oral cavity.* Antihistamines are drugs that act competitively with histamine. They are polar substances that have an amino group which becomes attached to receptors for histamine. Their structural configuration resembles the nitrogen-containing topical anesthetics in many respects. They possess one or more amino groups, are bases, and form salts with acids. Some antihistamines such as tripelennamine, are derived from ethylenediamine, and other antihistamines, such as diphenhydramine are derived from ethanolamine. The salts are highly ionized, poorly water soluble, and are not lipophilic. The bases are lipophilic and poorly ionized. Their absorption through the mucous membranes is similar to that of the "caine" and related nitrogen-containing topical anesthetics. Even though the structure of antihistamines, in may respects, resembles the general configuration characteristic of the "caine" type of topical anesthetic drugs, there is sufficient modification so that they do not manifest systemic effects similar to the "caine" drugs when they pass into the circulation.

The actions of antihistamines overlap with those of other drugs. Some have anticholinergic, antinauseant, and topical anesthetic activity. They act as anti-inflammatory agents when the inflammation is due to histamine release. Antihistamines that have

topical anesthetic/analgesic activity may be useful for relieving pain in preparations used in the oral cavity. There is little evidence that they are effective topically as antihistaminics. Any beneficial effects that may result are most likely due to the systemic effect from absorption from the mucous membranes of the mouth or throat or to any part of a dose that is swallowed. The antihistamines are furmulated as salts, such as the hydrochlorides. The buffering action converts the salts to the base form which is the active form. The base penetrates the mucous membranes and is easily absorbed. Most of the effects of a histamine are systemic. Some antihistamines have pronounced sedative effects and may cause drowsiness if used topically in oral health care preparations since they are absorbed and act systemically. Some have a central stimulating action, but this is not pronounced except in cases of overdosage.

References

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

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

(3) Adriani, J., and H. Dalili, "Penetration of Local Anesathetics Through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–840, 1971.

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

(5) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

(6) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association,* 183:711–716, 1964.

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

(8) Doty, R. W., and J. F. Bosma, "An Electromyographic Analysis of Reflex Deglutition," *Journal of Neurophysiology,* 19:44–60, 1956.

B. Categorization of Data

1. *Category I conditions under which oral health care anesthetic/analgesic agents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients.

Aspirin
Benzocaine
Benzyl alcohol
Dyclonine hydrochloride
Hexylresorcinol
Menthol
Phenol
Phenolate sodium
Salicyl alcohol

a. *Aspirin.* The Panel disagreed on important issues relevant to the safety and effectiveness of aspirin. Accordingly, part III, paragraph B.1.a.—Aspirin—consists of a majority report and a minority report. The minority report reflects the opinion of one Panel member.

(1) *Majority report on aspirin.* The Panel concludes that aspirin is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aspirin is the acetyl ester of salicylic acid (acetylsalicylic acid) (Ref. 1). Acetylsalicylic acid had been synthesized in 1899 by Dreser some years before it was introduced into medicine. It was first known as acetyl spiricum, from which the name aspirin is derived. Originally, it was obtained from a plant source, *Spiraea ulmaria.*

Aspirin is made by interacting acetic acid with salicylic acid. The acetic acid interacts with the hydroxyl group on the 2 position of salicylic acid. Aspirin is an odorless powder consisting of white, tubular or needlelike crystals (mostly monoclinic crystals, but orthorhombic and trichlinic crystals are at times encountered). It melts at approximately 135° C. In moist air, it is gradually hydrolyzed into salicylic and acetic acids and acquires the odor of acetic acid. It is stable in dry air (Ref. 2).

The dissolution of aspirin is a conditional process depending on the temperature of the water. One gram (g) dissolves in 300 mL water at 25° C, 100 mL water at 37° C (one 300-mg tablet of aspirin dissolves in 30 mL water at 37° C), 5 mL alcohol, 17 mL chloroform and 10 to 15 mL ether. When a commercially available aspirin tablet is dissolved (within the ratio mentioned above) the resulting fluid has the appearance of a suspension. Actually only the filler and binder are in suspension, while the acetylsalicylic acid is in solution. The filler can be separated by sedimentation and decantation or by filtration. When the remaining fluid is allowed to evaporate, the typical aspirin crystals will be obtained. When aspirin without filler is dissolved, the resulting fluid is clear. Evaporation will produce the typical aspirin crystals. Once the aspirin is in solution it will resist separation or crystallization when the temperature is lowered. No crystallization was observed when the aspirin solution was kept at −7° C for 16 hours (Ref. 3). It is decomposed by boiling water or when dissolved in solutions of alkali hydroxides and carbonates. Inorganic salts of acetylsalicylic acid are soluble in water, but are decomposed quickly (Ref. 4). Two polymorphic forms have been described. One form is prepared from a slow crystallization process at room temperature from a saturated solution of aspirin in 95 percent alcohol. This form melts between 143° and 144° C. The other form melts between 123° and 125° C. Tablets prepared from the product derived from the slow crystallization technique have a slower rate of dissolution than tablets prepared from the latter type of polymorph. There is evidence from the study of these two forms that aspirin crystals are converted to the less soluble form during dissolution. The study of aspirin in aqueous media has led to the suggestion that a phase change occurs on the surface of the crystals (Ref. 1).

Aspirin readily undergoes hydrolysis in aqueous solutions with the liberation of salicylic and acetic acids. In pure water complete decomposition takes place in 100 days. Acids hasten the rate of hydrolysis. The alkalis present in solutions of alkaline acetate and citrate dissolve aspirin, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Half the aspirin decomposes in about 4 days. The decomposition may be retracted somewhat by glycerin and sugar. Liquefaction occurs when aspirin is saturated with phenyl salicylate, acetanilid, phenacetin, aminopyrine, antipyrine, and other organic products. Partial hydrolysis occurs in mixtures of aspirin and hygroscopic substances of salts containing water of hydration. Even some talcs adversely effect the stability of aspirin (Ref. 5).

(i) *Safety.* The Panel concludes that aspirin is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aspirin applied topically to the skin is neither an irritant nor a counterirritant. However, it is irritating to the mucous membranes of the mouth and throat when the solid form is kept in contact with the mucosa for any length of time, either by design or accident. This has been known practically since the introduction of aspirin and is a well-established fact. Kawashima, Flagg, and Cox (Ref. 6) reported a case where

ulceration of the mucosa of the roof of the mouth resulted from the application of a tablet of aspirin by the patient for pain relief. The lesion healed promptly after aspirin medication was stopped. Roth et al. (Ref. 7) found that aspirin tablets remaining in contact with the roof of the mouth for one-half hour produced white, opaque buccal mucosal lesions which could be peeled off with slight pressure or by rubbing. They placed a quarter of a tablet each of plain, buffered, and combination tablets between the lower lip and the gum of 26 normal subjects for 30 to 60 minutes. The aspirin produced irregular lesions of sloughing and superficial necrosis of the mucous membranes of the mouth. In contrast to these observations, when a disc of cottonoid, 13 millimeters (mm) in diameter, saturated with a solution of aspirin without filler is placed on the mucosa of the lower lip and kept there for 60 minutes, no blanching of the mucosa or ulcerations was observed (Ref. 3). This procedure was repeated on 3 consecutive days, using approximately the same location, again without blanching or ulcerations. Reports of ulcerations with the use of aspirin-containing chewing gum could not be found. Ulcerations are, of course, also a possibility with this type of medication.

Aspirin has a free carboxyl group, but it is a weak acid. Aspirin is poorly absorbed from the mouth, but it is readily absorbed from the stomach since it is nonionized in this form. In the intestines, it is absorbed as the acetylsalicylate ion. Peak serum levels are reached in 1 to 2 hours after oral ingestion. Blood levels do not necessarily correlate with the degree of analgesia. Half or more of the blood-borne aspirin is bound to plasma proteins, especially albumin, by means of the carboxyl group. The drug is very rapidly distributed to all body tissues. It is excreted very rapidly, although traces continue to be excreted for several days. In febrile patients, a proportion is eliminated unchanged, to some extent, but most is converted to salicyluric acid. Smaller amounts of the drug are eliminated as salicylic acid and also as conjugates with glucuronic acid to form glucuronates. Some of the drug is eliminated as gentisic acid.

Aspirin is not highly toxic when taken orally or given parenterally notwithstanding the voluminous literature on poisoning by the drug. When the widespread use of aspirin is taken into consideration, the total number of cases of poisoning that occur is small when they are extrapolated to the number of doses used. A single dose of 10 to 30 g aspirin may be fatal in an adult, although less than 1 g aspirin has killed and 130 g have been tolerated (Ref. 8). Children (especially under the age of 3 years) are disproportionately more susceptible than adults to the toxic action of salicylates (Ref. 9). Impaired renal function accentuates toxicity.

A total of 12 g ingested during 24 hours usually produces symptoms of salicylism, i.e., tinnitus, vertigo, impaired hearing, and headache. More severe manifestations include hyperpnea, fever, metabolic acidosis, and, less regularly, dimness of vision, sweating, thirst, vomiting, gastrointestinal hemorrhage, diarrhea, skin rashes, tachycardia, restlessness and delirium, depression, stupor, coma, cardiovascular collapse, convulsions, and respiratory failure. Fatal cases show diffuse endothelial changes with petechial hemorrhages and congestion through the viscera (Ref. 10).

One of the untoward effects following oral administration of aspirin is its propensity to cause bleeding, particularly of the gastric mucosa. The extent of blood loss from the stomach is dose related. This effect, which reportedly occurs in 70 percent of the patients taking repeated doses of aspirin, has been studied by determining the fecal blood loss in healthy human volunteers injected with radioactive chromium-51 tagged red blood cells (Ref. 11). The radioactivity of the stools provided data which were used to plot the amount of blood loss. Prior to administration of 0.3 g aspirin, the average daily blood loss in a group of volunteers was 0.3 mL per individual. With doses of aspirin of 2.6 g daily, the average loss was increased to 2.3 mL per individual. When doses of 4.5 g aspirin were administered daily, losses increased to 6 mL per individual.

Aspirin may cause ulcerations of the mucosa of the stomach. This is believed to be due to the fact that it is un-ionized in the acid medium (pH less than 2) in the stomach and passes through the lipid barrier of the mucosal cells. Once in the cells, where the pH is close to 7, it becomes ionized and hydrolyzes to salicylic and acetic acids.

Macerations are far less frequent in the intestines because the pH is close to 7 and passage into the intestinal mucosal cells is limited, since the aspirin in the lumen is ionized. Less drug concentrates in these cells.

Since the administration of aspirin causes an increase in bleeding time from an average of 2.6 minutes during the control period to an average of 4.5 minutes when aspirin was given to the aforementioned subjects (Ref. 11), the question of whether gastrointestinal bleeding is due to the local effect on the mucosa of the stomach or to a systemic effect related in prolongation of bleeding time, has been the subject of considerable debate. That it is a local effect appears to be established by the fact that when sodium salicylate is injected intravenously, gastrointestinal bleeding does not occur. Bleeding time is prolonged to approximately the same degree whether aspirin is given orally or parenterally. The importance of recognizing this untoward effect of aspirin in patients with hemostatic abnormalities and clotting defects has been stressed and documented in many reports, although bleeding time prolongation has been ascribed to a defective vascular response. Others attribute it to a decrease in blood platelet aggregation. Following injury to a capillary, endogenous adenosine diphosphate is released from platelets causing an irreversible aggregation which results in the formation of a plug that is primarily responsible for the arrest of bleeding. Aspirin apparently inhibits the release of endogenous adenosine diphosphate, thereby prolonging bleeding time. As little as 5 g aspirin can produce this type of platelet defect, and the abnormality persists anywhere from 4 to 7 days, corresponding to the life-span of the platelets. Since aspirin is absorbed to some extent through the oral and pharygeal mucous membranes and circulates in the blood, this effect upon coagulation is of importance, particularly since it is used in mouthwashes and in chewing gum.

Late post-tonsillectomy hemorrhages have been attributed to the use of aspirin in tablet or chewing gum form, while no bleeding was seen with acetaminophen (Ref. 12).

The Panel feels that the use of aspirin orally or topically in patients who have a bleeding tendency or after dental or throat surgery may be unwarranted and recommends that a warning be placed on the label stating: "Do not use if you have a bleeding problem or after dental or throat surgery."

The exact relationship between ulcerogenic potential in the mouth and that in the stomach has not been established since the pH of saliva is below 6, while that of the gastric juice is less than 2. It is felt that the adverse reactions are basically the result of the acetyl group.

Two types of systemic adverse reactions may occur from aspirin, the idiosyncratic type and the allergic type. Idiosyncrasy to aspirin is rare. It does occur, however, and the symptoms differ from the allergic type of response. The

idiosyncratic reaction is not of the immunologic-type reaction, but is believed to be due to disturbances in prostaglandin synthesis. As is the case with any other drug, aspirin can act as a hapten and produce sensitization. Sensitization is most frequently observed in high-risk allergic (atopic) individuals, particularly in asthmatics, and especially in those with nasal polyps (Refs. 13 and 14). The manifestations of an allergic response are urticaria, erythema, desquamatative, bullous, or purpural skin lesions, angioneurotic edema, laryngeal stridor, asthma, and peripheral vascular collapse. Absorption of aspirin from mucous membranes may produce a systemic allergic response. These reactions are often serious and fatal.

In summary, then, the Panel feels that aspirin should not be used either systemically or topically following operative procedures of the mouth or throat, when the mucous membranes are highly inflamed or abraded, when there are eroded lesions that are bleeding, or when the patient is on anticoagulant medication because aspirin interferes with the clotting mechanism and bleeding may result.

(ii) *Effectiveness.* The Panel concludes that aspirin is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The Panel concludes that aspirin has a local analgesic effect in the oral cavity (Ref. 3). It is useful in relieving mild to moderate pain, not only when the pain is localized, but also when it is generalized. There is evidence that some of the pain relief obtained from orally ingested aspirin is due to a peripheral effect. Since salicylates exert an anti-inflammatory effect, part of the pain relief may be also due to preventing or reducing the inflammation and thereby removing one of the sources of the stimuli to the pain receptors. Lim et al. (Ref. 15) noted that salicylates apparently block painful stimulation of visceral receptors caused by intra-arterially or intraperitoneally injected bradykinin. They postulate that the analgesic effect is due to blockage of chemoreceptors mediating pain. Whether the salicylate effect is confined to endothelial and mesothelial structures where bradykinin may be a mediator of pain is still not known. More recent data indicate that salicylates act by preventing local inflammation not due to bradykinin (Refs. 16 through 19). Scott (Ref. 20) reports that topical application of aspirin inhibits steady-state discharge and response to a brief heat stimulus. He was able to terminate the local effect by washing the aspirin out of the dental socket.

Many diverse statements have been made regarding the mechanism of action of aspirin. This is quite understandable since aspirin has a wide range of actions. It is, therefore, necessary to state to which action reference is made. According to current knowledge, the analgesic action of aspirin is peripheral (Refs. 21 through 24) and topical (Refs. 3 and 20). The antipyretic action is central, located in the preoptic, anterior hypothalamic region (Ref. 25). The perspiration accompanying a fever is a peripheral mechanism. A local effect, in addition to the analgesic effect, is also demonstrated by desquamation and by local mucosal erosions (the so-called "aspirin burn"). Tissue damage and bleeding are significantly influenced by the general status of the patient, including such conditions as blood dyscrasia, vitamin K deficiency, anticoagulants, and alcoholism. Whether or not aspirin is actually completely dissolved will also influence tissue damage (Ref. 3). The importance of adequate fluid intake with aspirin medication cannot be stressed enough (Ref. 3).

The Panel accepts that the analgesic action of aspirin is peripheral and topical.

(iii) *Dosage.* The topical dosage of aspirin is incorporated in a chewing gum base. Adults: Chew 420 mg of aspirin as needed, not to exceed 3,360 mg in 24 hours. Children 6 to under 12 years of age: Chew 210 to 420 mg of aspirin as needed, not to exceed 1,680 mg in 24 hours. Children 3 to under 6 years of age: Chew 210 mg of aspirin as needed, not to exceed 630 mg in 24 hours. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(iv) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following specific labeling:

Warnings. (*a*) "Do not use if you are sensitive or allergic to aspirin."

(*b*) "Do not use if you have a bleeding problem or if you are taking an anticoagulant drug."

(*c*) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(*d*) "Do not use after surgery in the mouth or throat."

(*e*) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 160–164, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck, and Co., Rahway, NJ, p. 114, 1976.

(3) Minutes of the Advisory Review Panel on OTC Oral Cavity Drug Products, 27th Meeting, August 14, 1979, and 28th Meeting, December 12, 13, and 14, 1979.

(4) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, pp. 12–13, 1968.

(5) Gold, G., and J. A. Campbell, "Effect of Selected U.S.P. Talcs on Acetylsalicylic Acid Stability in Tablets," *Journal of Pharmaceutical Sciences,* 53:52–54, 1964.

(6) Kawashima, Z., R. H. Flagg, and D. E. Cox, "Aspirin-induced Oral Lesion: Report of Case," *Journal of the American Dental Association,* 91:130–131, 1975.

(7) Roth, J. L. A., et al., "Topical Action of Salicylates in Gastrointestinal Erosion and Hemorrhage," *Gastroenterology,* 44:146–158, 1963.

(8) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins Baltimore, section III, p. 209, 1969.

(9) Erganian, J. A., G. B. Forbes, and D. M. Case, "Salicylate Intoxication in the Infant and Young Child: A Report of Thirteen Cases," *Journal of Pediatrics,* 30:129–145, 1947.

(10) Woodbury, D. M., and E. Fingl, "Analgesic-Antipyretics, Anti-inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 326–339, 1975.

(11) "Soluble, Buffered Aspirin Sought to Eliminate Blood Loss in Stomach," *Journal of the American Medical Association,* 209:17–18, 1969.

(12) Fox, S. L., and G. B. West, "Vitamin K and Late Tonsillar Hemorrhage," *Laryngoscope,* 51:564–574, 1947.

(13) Speer, F., "Aspirin Allergy: A Clinical Study," *Southern Medical Journal,* 68:314–318, 1975.

(14) Fein, B. T., "Aspirin Shock Associated with Asthma and Nasal Polyps," *Annals of Allergy,* 29:598–601, 1971.

(15) Lim, R. K. S., et al., "Site of Action of Narcotic and Non-narcotic Analgesics Determined by Blocking Bradykinin-Evoked Visceral Pain," *Archives Internationales de Pharmacodynamie et de Therapie,* 152:25–58, 1964.

(16) Vane, J. R., "Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs," *Nature: New Biology,* 231:232–235, 1971.

(17) Vane, J. R., "Mode of Action of Aspirin and Similar Compounds" *in* "Prostaglandin Synthetase Inhibitors—Their Effects on Physiological Functions and Pathological States," edited by H. J. Robinson and J. R.

Vane, Raven Press, New York, pp. 155–163, 1974.

(18) Vane, J. R., "Prostaglandins as Mediators of Inflammation," *in* "Advances in Prostaglandin and Thromboxane Research: Volume 2," edited by B. Samuelsson and R. Paoletti, Raven Press, New York, pp. 791–801, 1976.

(19) Vane, J. R., "The Mode of Action of Aspirin-like Drugs," *Agents and Actions,* 8:430–431, 1978.

(20) Scott, D., Jr., "Aspirin: Action on Receptor in the Tooth," *Science,* 161:180–181, 1968.

(21) Lim, R. K. S., "Salicylate Analgesia," *in* "The Salicylates," edited by M. J. H. Smith and P. K. Smith, Interscience Publishers, New York, pp. 155–202, 1966.

(22) Davison, C., and H. G. Mandel, "Nonnarcotic Analgesics and Antipyretics I: Salicylates," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J. R. DiPlama, McGraw-Hill Book Co., New York, pp. 379–403, 1971.

(23) Woodbury, D. M., and E. Fingl, "Analgesic-Antipyretics, Anti-inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 326–327, 1975.

(24) Hollister, L. E., "Neurologic Disorders," *in* "Clinical Pharmacology: Basic Principles in Therapeutics," 2d Ed., edited by K. L. Melmon and H. F. Morrelli, Macmillan Publishing Co., pp. 881–884, New York, 1978.

(25) Wit, A., and S. C. Wang, "Temperature-Sensitive Neurons in Preoptic/Anterior Hypothalamic Region: Actions of Pyrogen and Acetylsalicylate," *American Journal of Physiology,* 215:1160–1169, 1968.

(2) *Minority report on aspirin.* The minority of the Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of aspirin as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The minority emphasizes that it is evaluating aspirin as an ingredient for topical use and is evaluating the ingredient per se and not any particular formulation.

Aspirin is the acetyl ester of salicylic acid (acetylsalicylic acid) (Ref. 1). Acetylsalicylic acid had been synthesized in 1899 by Dreser some years before it was introduced into medicine. It was first known as acetyl spiricum, from which the name aspirin is derived. Originally, it was obtained from a plant source, *Spiraea ulmaria.*

Aspirin is made by interacting acetic acid with salicylic acid. The acetic acid interacts with the hydroxyl group on the 2 position of salicylic acid. Aspirin is an odorless powder consisting of white, tubular, or needle-like cyrstals. It melts at approximately 135° C. In moist air, it slowly hydrolyzes to salicylic and acetic acids and acquires the odor of acetic acid. One gram dissolves in approximately 300 mL water at 25° C, in 100 mL at 37° C, 5 mL alcohol, 17 mL chloroform, and 10 to 15 mL ether at 25° C. Two polymorphic forms have been described. One form is prepared by a slow crystallization process at room temperature from a saturated solution of aspirin in 95 percent alcohol. This form melts between 143° and 144° C. The other form is obtained simply from evaporation of a hexane solution. It melts between 123° and 125° C. Tablets prepared from the product derived from the slow crystallization technique have a slower rate of dissolution than tablets prepared from the latter type of polymorph. There is evidence from the study of these two forms that aspirin crystals are converted to the less soluble form during dissolution. The study of aspirin in aqueous media has led to the suggestion that a phase change occurs on the surface of the crystals (Ref. 1).

Aspirin readily undergoes hydrolysis in aqueous solutions with the liberation of salicylic and acetic acids. In pure water, complete decomposition takes place in 100 days. Acids hasten the rapidity of hydrolysis. The alkalis present in solutions of alkaline acetate and citrate dissolve aspirin, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Half the aspirin decomposes in about 4 days. The decomposition may be retarded somewhat by glycerin and sugar. Liquefaction occurs when aspirin is saturated with phenyl salicylate, acetanilid, phenacetin, aminopyrine, antipyrine, and many other organic products. Partial hydrolysis occurs in mixtures of aspirin and hydroscopic substances or salts containing water of hydration. Even some talcs adversely effect the stability of aspirin (Ref. 2). Aspirin decomposes when dissolved in solutions of alkali hydroxides and carbonates. It forms a methyl and phenyl ester and inorganic salts. Inorganic salts decompose readily when dissolved in water, especially the calcium salt. It forms a sodium salt (Ref. 3).

(i) *Safety.* The minority of the Panel concludes that there are insufficient data to classify aspirin as a safe OTC analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Aspirin applied topically to the skin is neither an irritant nor a counterirritant. However, it is irritating to all the surface mucosal cells lining the gastrointestinal tract including the mucous membranes of the mouth and throat (42 FR 3538). Kawashima, Flagg, and Cox (Ref. 4) in 1975 reported that aspirin tablets applied directly to the mucous membranes of the mouth for a local analgesic effect caused lesions of the mucous membranes of the roof of the mouth. Roth et al. (Ref. 5) found that aspirin tablets remaining in contact with the roof of the mouth for one-half hour produced white, opaque buccal mucosal lesions capable of being peeled off with slight pressue or by rubbing. They placed a quarter of a tablet of plain, buffered, and combination tablets between the lower lip and the gum of 26 normal subjects for 30 to 60 minutes. In every case the aspirin produced irregular lesions of sloughing and superficial necrosis of the mucous membranes of the mouth. Aspirin incorporated in chewing gum has produced severe lesions of the inner wall of the cheek which promptly healed when use of the preparation was discontinued (Refs. 4 and 6).

Aspirin has a free carboxyl group, but it is a weak acid which combines with metallic ions to form salts and with organic radicals to form esters, as mentioned above. Aluminum aspirin, used as an internal analgesic, is insoluable in water. Aspirin is poorly absorbed from the mouth, but it is readily absorbed from the stomach since it is nonionized in this form. In the small intestine, it is absorbed as the acetylsalicylate ion. Peak serum levels are reached in 1 to 2 hours after oral ingestion. Blood levels do not necessarily correlate with the degree of analgesia. Half or more of the blood-borne aspirin is bound to plasma proteins, especially albumin, by means of the carboxyl group. The drug is very rapidly distributed to all body tissues. Aspirin is excreted very rapidly, although traces continue to be excreted for several days. In febrile patients, a proportion is eliminated unchanged, to some extent, but most of it is converted to salicyluric acid. Smaller amounts of the drug are eliminated as salicylic acid and also as conjugates with glucuronic acid to form glucuronates. Some of the drug is eliminated as gentisic acid.

Aspirin is not highly toxic systemically when taken orally or given parenterally notwithstanding the voluminous literature on poisoning by the drug. Much of the poisoning is accidental and occurs in children. When the widespread use of aspirin is taken into consideration, the total number of cases of poisoning that occur is small when they are extrapolated to the number of doses used. A single dose of 10 to 30 g aspirin may be fatal, although survival has been reported when much

larger doses have been ingested. Deaths from smaller doses have been reported. Impaired renal function accentuates toxicity. A total of 12 g aspirin ingested during 24 hours usually produces symptoms of salicylism, i.e., tinnitus, vertigo, impaired hearing, and headache. More severe manifestations include hyperpnea, fever, metabolic acidosis, and, less regularly, dimness of vision, sweating, thirst, vomiting, diarrhea, skin rashes, tachycardia, restlessness, and delirium. Salicylism may resemble diabetic and renal disorders. Numerous cases of depression, stupor, coma, cardiovascular collapse, convulsions, and respiratory failure follow salicylism. Fatal cases show diffuse endothelial changes with petechial hemorrhages and congestion through the viscera (Ref. 7).

One of the untoward effects following oral administration of aspirin is its propensity to cause mucosal bleeding, particularly of the gastric mucosa. The extent of blood loss from the stomach is dose related. This effect, which reportedly occurs in 70 percent of patients taking repeated doses of aspirin, has been studied by determining the fecal blood loss in healthy human volunteers injected with radioactive chromium-51-tagged red blood cells. The radioactivity of the stools provided data for determinig the degree of blood loss. Prior to administration of 0.3 g aspirin, the average daily blood loss in one group of volunteers was 0.3 mL per individual. With doses of aspirin of 2.6 g daily, the average loss was increased to 2.3 mL per individual. When doses of 4.5 g aspirin were administered daily, losses increased to 6 mL per individual (Ref. 8).

Aspirin causes ulcerations of the mucosa of the stomach. This is believed to be due to the fact that it is un-ionized in the acid medium (pH less than 2) in the stomach and passes through the lipid barrier of the mucosal cells. Once in the cells, where the pH is close to 7, it becomes ionized and hydrolyzes to salicylic and acetic acids. Ulcerations occur less frequently in the intestines and on other mucosal surfaces because the pH is close to 7 and passage into the mucosal cells is limited, since the aspirin is ionized. Less drug concentrates in these cells.

The question of whether gastrointestinal bleeding is due to a local effect on the mucosa of the stomach or to a systemic effect related to prolongation of bleeding time has been the subject of considerable debate. That it is a local effect appears to be established by the fact that when aspirin as a sodium salt (not sodium salicylate) is injected intravenously, gastrointestinal bleeding does not occur. Apparently, the presence of the acetyl group is essential for this response (Ref. 9). The administration of aspirin caused an increase in bleeding time from an average of 2.6 minutes during the control period to an average of 4.5 minutes when aspirin was given to test subjects (Ref. 8). Bleeding time is prolonged to approximately the same degree whether aspirin is given orally or parenterally. This bleeding time increase is ascribed to a decrease in circulating prothrombin. It also occurs after the administration of sodium salicylate. Apparently the presence of the acetyl group is not necessary to cause prolongation of bleeding time due to hypoprothrombinemia. The importance of recognizing this untoward effect of aspirin in patients with hemostatic abnormalities and clotting defects has been stressed and documented in many reports.

Aspirin also causes a decrease in blood platelet aggregation. Following injury to a capillary, endogenous adenosine diphosphate is released from platelets causing an irreversible aggregation which results in the formation of a plug that is primarily responsible for the arrest of bleeding. Aspirin apparently inhibits the release of endogenous adenosine diphosphate, thereby prolonging bleeding time. As little as 5 g aspirin can produce this type of platelet defect and the abnormality persists anywhere from 4 to 7 days, corresponding to the life-span of the platelets. Inhibition of platelet aggregation does not occur when sodium salicylate is administered. Apparently the presence of the acetyl group is necessary for this adverse response to occur. Since aspirin is absorbed to some extent through the oral and pharyngeal mucous membranes and circulates in the blood, this effect upon coagulation is of importance particularly since it is used in gargles, chewable tablets, and in chewing gum.

Locally applied aspirin may produce massive hemorrhage from capillary beds of tissue other than that of the gastric mucosa, such as the tonsillar areas of the throat. Several cases of massive hemorrhage from the tonsillar bed following topical application of a gargle of aspirin-containing chewing gum have been reported (Refs. 10 and 11). Hemorrhage was observed in 8 percent of 100 posttonsillectomy patients medicated with aspirin (Ref. 12). The bleeding occurred on the sixth or seventh postoperative day. No bleeding occurred in 100 patients medicated with acetaminophen. A high incidence of posttonsillectomy bleeding was reported by Fox and West (Ref. 13) in children given an aspirin-containing chewing gum. The incidence of bleeding ceased when use of the gum was discontinued. Hersh (Ref. 14) noted more bleeding among patients undergoing dental extractions who received aspirin than those who received acetaminophen preoperatively.

The exact relationship between ulcerogenic potential in the mouth and that in the stomach has not been established. The pH of saliva is seldom below 6 and the aspirin is ionized and not absorbed, while that of the gastric juice is less than 2 and the aspirin is un-ionized and readily absorbed. Apparently the presence of the hydrogen ion is not essential for this reaction to occur.

The minority of the Panel feels that the use of aspirin topically or orally in patients with lesions in the mouth that may bleed may be unwarranted and recommends that a warning be placed on the labeling stating, "Do not use if you have bleeding problems."

Two types of systemic hypersensitivity reactions may occur from aspirin, the idiosyncratic type and the allergic type. Idiosyncrasy to aspirin is rare. It does occur, however, and the symptoms differ from the allergic type of response. The triad of idiosyncrasy, nasal polyps, and late onset of asthma are the usual manifestations. The idiosyncratic reaction is not an immunologic-type reaction, but is believed to be due to disturbances in prostaglandin synthesis. As is the case with any other drug, aspirin can act as a hapten and produce both systemic and local sensitization. Sensitization is most frequently observed in high-risk allergic (atopic) individuals, particularly in asthmatics (Refs. 15 and 16). The manifestations of a local sensitization are erythema, desquamatative, bullous, or purpural skin lesions. The manifestations of systemic sensitization are angioneurotic edema, laryngeal stridor, asthma, and peripheral vascular collapse. Absorption of aspirin from mucous membranes of the mouth and throat may produce any of the above responses. Some of these reactions are often serious and may be fatal. (See part II. paragraph E. above—Adverse Reactions.)

In summary then, the minority of the Panel believes that aspirin is not desirable and is not always safe and should not be used topically for symptomatic relief of conditions of the mouth and throat. The minority of the Panel feels it should not be used to treat conditions in which the mucous membranes are highly inflamed or abraded because aspirin is irritating to

mucosal surfaces. The minority of the Panel also believes that aspirin should not be used following operative procedures of the mouth or throat or for eroded lesions that are oozing blood, because the drug interferes with clotting mechansims, and bleeding may be enhanced.

(ii) *Effectiveness.* The minority of the Panel concludes that there are insufficient data available to permit final classification of the effectiveness of aspirin as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within in the proposed dosage limit set forth below.

Aspirin is the most widely used OTC internal analgesic ingredient in the United States (Ref. 9). In view of its immense popularity in this country, it has been extensively discussed in the medical and scientific literature. Aspirin is useful as a systemically acting analgesic to relieve mild to moderate pain, not only when the pain is localized, but also when it is generalized. Thousands of articles have been written concerning aspirin since the first pharmacologic data were reported in the literature in 1899.

Aspirin possesses no known topical anesthetic activity and does not block transmission of nerve impulses by altering the neuronal membranes as do topical anesthetics such as benzocaine, tetracaine, and lidocaine (Ref. 17). It, therefore, exerts no known anesthetic or analgesic effect on the skin or mucous membranes. Gargling with solutions of aspirin produces irritation and burning sensations, particularly if the solutions are concentrated, instead of a numbing effect which aspirin should do if it were a local anesthetic.

The chemical structure of aspirin in no way resembles the structure of the hydroxy or nitrogenous types of local anesthetics. Indeed, the introduction of a carboxyl group on a structure known to possess local anesthetic activity, as for example cocaine, nullifies its local anesthetic activity. Removal of the methyl group from ecgonine leaves a free carboxyl group on the structure of cocaine and nullifies its local anesthetic activity (Ref. 19). Aspirin is also nonionized at very low pH's such as that of the stomach. At the pH of the oral cavity it is ionized and would be less inclined to be absorbed and to pass through the mucous membranes of the mouth and throat and into the lipid sheath of a nerve fiber. Impulse conduction along peripheral nerves is not affected by salicylates (Ref. 17). The interference with absorption due to the fact that aspirin is ionized would negate any possibility that it acts directly to antagonize the effects of bradykinin or prostaglandins in the submucosal tissues.

Aspirin, as is the case with other internal analgesics, acts centrally at thalamic and subcortical areas. However, there is evidence that some of the pain relief obtained from orally ingested aspirin is due to a peripheral effect of the blood-borne drug (Ref. 17). Since salicylates exert an anti-inflammatory effect, part of the pain relief appears to be due to preventing or reducing the inflammation and removal of one of the sources of the stimuli to the pain receptors. However, this viewpoint is not substantiated by the fact that blood-borne phenacetin and acetaminophen are analgesic but lack significant anti-inflammatory properties, while phenylbutazone is an effective anti-inflammatory agent, but possesses feeble analgesic properties. Lim and associates (Ref. 19) noted that salicylates apparently block painful stimulation of visceral receptors caused by intra-arterially or intraperitoneally injected bradykinin. They postulate that the analgesic effect is due to blockage of chemoreceptors mediating pain. Whether the salicylate effect is confined to endothelial and mesothelial structures where bradykinin may be a mediator of pain is still not known. More recent data indicate that salicylates act by preventing the synthesis of prostaglandins, thereby alleviating or preventing local inflammation which is not due to antagonizing the effects of bradykinin (Ref. 9). These concepts relate to the blood-borne drug in the tissues and are not supportive evidence of a direct local action caused by penetration of the aspirin into the mucous membranes. Gastric absorption and not local transfer is mentioned in these studies. Scott (Ref. 20) reported that topical application of aspirin to dentinal receptors in cats inhibits both steady-state discharge and response to a brief heat stimulus. The minority of the Panel notes that these studies were done on dentine and not mucous membranes.

Chewing gum formulations containing aspirin in a gum base have developed supposedly to provide a greater retention and absorption of the drug and to produce a topical local effect on the surrounding tissue. One marketed preparation bears the labeling "for the relief of minor sore throat pain, muscular aches, and pain." Although the labeling does not specifically state that the effect is relief of sore throat due to the topical application of the aspirin, the user of such a product cannot help inferring that this is what is meant. Data in the submission for the product do not adequately support this contention. The minority of the Panel concurs with the sentiments of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products which states as follows in the **Federal Register** July 8, 1977 (42 FR 35376–35377).

Historically, aspirin has been used as a gargle for the treatment of minor sore throat pain. Chewing gum formulations containing aspirin in a gum base were developed to provide for greater retention and absorption of the drug and to produce a topical, local effect on the surrounding tissues. These formulations may also make the medication more pleasant to take. Chewing gums with aspirin are primarily used and labeled for "relief of minor sore throat pain." However, other traditional labeling is also included such as "for headache, muscular aches, and pain." The latter claims can only be attributed to the absorption of the drug into the systemic circulation.

The Panel concludes that aspirin or any analgesic in a gum base, with the specific claims for the relief of sore throat, has not been adequately tested for effectiveness. This use of aspirin may not be desirable or safe particularly if the tissue is highly inflamed or abraded because aspirin is irritating to the mucosal tissue as discussed above. The Panel recommends that claims of aspirin-containing gum for the relief of sore throat or the use of aspirin as a gargle for a local effect properly belongs in a review of ingredients claimed for treatment of sore throat in general and should therefore be deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products for evaulation.

The Panel finds marketing of an OTC analgesic, in a chewing gum formulation, acceptable if the product contains the dosage and Category I labeling claims recommended by the Panel. However, such product formulations containing aspirin should include the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advise and supervision of a physician." As with chewable tablets discussed above, oral mucosal damage may occur from the use of chewing gum aspirin products and this effect of aspirin on blood clotting may be a factor in such situations.

The minority of the Panel has examined the data in the subjective study conducted by Bernstein and Nelson (Ref. 2). In this study 20 patients with evidence of sore throat and pharyngitis were given aspirin in a gum vehicle and a placebo. Pain was induced by having the subjects chew a cracker and swallow with water. Although the submitted data indicate that the subjects felt less pain after taking the gum containing aspirin and preferred this preparation to the placebo, the minority of the Panel does not feel that the study proves that the pain relief reported was due to a local anesthetic effect on pain receptors in the throat and not from a systemic action of the absorbed aspirin.

The minority of the Panel agrees with the OTC Advisory Review Panel on Internal Analgesic and Antirheumatic Products that aspirin in a gum base with specific claims for relief of sore throat by a topical action has not been adequately studied, and that there is much evidence indicating that it is without appreciable topical analgesic effect and that the effect is probably a systemic one due to the aspirin that is swallowed and absorbed. The topical use of aspirin may not be desirable or safe, particularly if the tissues are highly inflamed or abraded, because aspirin is irritating to the mucosal tissue. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, in the **Federal Register** of December 4, 1979 (44 FR 69845–69847), has likewise concluded that even though percutaneous absorption of salicylate does occur, its action is systemic when topically applied and not local on the receptors for pain. Some degree of percutaneous absorption of salicylate esters occurs through the intact skin (Refs. 1, 22, and 23), but no significant cutaneous analgesic or anesthetic activity has been demonstrated. Likewise some absorption occurs from the normal mucous membranes. No controlled studies exist demonstrating that the relief of pain is due to topical application. Any analgesic effect that is obtained is due to the systemic effect that follows absorption from the stomach and oral mucous membrane after topical use. Aspirin is the best absorbed of all salicylates percutaneously from aqueous and other solutions. The percutaneous absorption of aspirin is increased 30 percent when 2 percent camphor is present. In a statement attributed to Fantus (Ref. 24), it is said that the absorption of salicylates through the skin is increased if the solution contains 20 percent alcohol. There is no indication that there is any correlation between these findings concerning absorption from the skin and the absorption of asprin from the mucous membranes of the oral cavity. Blood levels of salicylates have been demonstrated after cutaneous application using tracer elements in animals. Excretion of salicylates and metabolites into the urine have been demonstrated after percutaneous absorption and absorption from the mucous membranes. Comparison of blood levels following topical application on the oral and pharyngeal mucous membranes with those following oral ingestion of therapeutic doses have not been made.

One Panel member made an oral presentation on a particular commercial product containing aspirin in chewing gum at the August 14, 1979 meeting of the Advisory Review Panel on OTC Oral Cavity Drug Products (Ref. 25). The Panel member stated that aspirin in chewing gum is effective as a topical analgesic. No written submission was presented to the Panel. The minority of the Panel could not evaluate the data presented in such a manner. The Panel member was told to submit a report for distribution to the Panel and that the data would be analyzed statistically by FDA for validity. No submission was received by FDA or any Panel member for study and evaluation of data submitted from personal experimentation using the "Adriani Method." How the method was used, the type of subjects studied, and other pertinent data were not presented. If they were, they were unclear to the minority of the Panel.

At the final Panel meeting the subject was discussed further and the same Panel member discussed the effectiveness of the same commercial product and presented views which, to the minority of the Panel, appeared to reflect private opinions rather then scientific facts (Ref. 26).

Adriani, Minokadeh, and Naraghi (Ref. 27) have studied the analgesic effects of a saturated solution of aspirin swabbed on the forepart and tip of the tongue using the method of Adriani and Zeppernick. Pain was induced with a direct electric current of a pulsatile type of 20 cycles per second and at a voltage range of 1 to 5 volts. The study was double-blinded and performed on 10 adult healthy volunteers. Saline was used as a control (placebo). Initially, every subject complained of a stinging sensation when the aspirin was applied. This disappeared after several minutes. However, no sensation of numbness developed at any time. The aspirin was not more effective in abolishing the painful stimulus than the placebo. Benzocaine in propylene glycol was swabbed over the same area after completion of the testing. In each case, after the use of placebo and the aspirin, numbness resulted from the use of the benzocaine. A saturated solution of acetaminophen was applied in the same manner as aspirin. No burning sensation was experienced by any subject. Likewise, there was no diminution in response to pain. The response to aspirin was the same as with acetaminophen and the placebo. It is obvious from these data that aspirin possesses no local analgesic or anesthetic activity.

The minority of the Panel concludes from available data that the action of aspirin applied topically is systemic and that any analgesic effect is due to the blood-borne drug that is absorbed. The minority of the Panel finds no data to substantiate claims that blood levels following topical application of aspirin on the skin or mucous membranes are sufficient to produce topical analgesia or anesthesia.

The minority of the Panel accepts the fact that aspirin acts in a dual manner in producing analgesia; one acting centrally in the brain and one acting peripherally by the blood-borne drug acting as an anti-inflammatory agent. It does not support the assumption that is made that the drug penetrates the mucous membranes and exerts its effects topically on the pain receptors and other structures beneath the mucosa or neutralizes such substances as bradykinin or prostaglandins directly by passage through the inflamed mucous membranes.

In the **Federal Register** of July 8, 1977 (42 FR 35375–35376), the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products stated:

> Chewable tablets offer a convenient method of administering the drug to individuals who have difficulty in swallowing whole tablets. This dosage form is especially popular for use in children. There are many marketed children's chewable aspirin tablets, which are usually flavored, containing 80 mg (1.23 gr) of aspirin per dosage unit. These tablets may be chewed, crushed on a spoon, dissolved on the tongue, or even swallowed as a conventional tablet. The Panel finds these chewable, flavored tablets acceptable and recommends that all such tablets containing salicylates for children under 12 years be labeled, "Drink water with each dose." In addition, as noted elsewhere in this document, because aspirin can increase bleeding, the Panel recommends that chewable aspirin-containing tablets be labeled with the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician."

The minority of the Panel notes that washing with water after chewing the tablets is advised presumably to avoid prolonged contact and aspirin burns.

It is consensus of the minority of the Panel that the topical use of aspirin in any form is unwarranted and unjustified. Reasons for this include the possible injury to the mucosa of the mouth and throat, the paucity of data on effectiveness as a topical analgesic, the possibility of bleeding problems, and because safer and more effective agents are available for relief of pain of sore throat and sore mouth.

(iii) *Proposed dosage.* Adults and children 3 years of age and older: 130 to 500 mg of aspirin per unit, incorporated in a chewing gum base; chew 1 gum tablet every 4 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *Labeling.* The minority of the Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the minority of the Panel recommends the following specific labeling:

Warnings—(*a*) "Do not use if you are sensitive or allergic to aspirin."

(*b*) "Do not use if you have bleeding problems."

(*c*) "Do not use without a physician's advice if your mouth or throat is highly irritated, inflamed, or ulcerated."

(*d*) "Do not use if you have stomach ulcers."

(*v*) *Evaluation.* Data to demonstrate effectiveness should be required in accordance with the guidelines set forth below for OTC oral health care anesthetic/analgesic active ingredients. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 160–164, 1973.

(2) Gold, G., and J. A. Campbell, "Effects of Selected U.S.P. Talcs on Acetylsalicylic Acid Stability in Tablets," *Journal of Pharmaceutical Science,* 53:52–54, 1964.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 114, 1976.

(4) Kawashima, Z., R. H. Flagg, and D. E. Cox, "Aspirin-induced Oral Lesion: Report of Case," *Journal of the American Dental Association,* 91:130–131, 1975.

(5) Roth, J. L. A., et al., "Topical Action of Salicylates in Gastrointestinal Erosion and Hemorrhage," *Gastroenterology,* 44:146–158, 1963.

(6) Claman, H. N., "Mouth Ulcers Associated with Prolonged Chewing of Gum Containing Aspirin," *Journal of the American Medical Association,* 202:651–652, 1967.

(7) Woodbury, D. M., and E. Fingl, "Analgesic-Antipyretics, Anti-inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 326–339, 1975.

(8) "Soluble Buffered Aspirin Sought to Eliminate Blood Loss in Stomach," *Journal of the American Medical Association,* 209:17–18, 1969.

(9) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 99–106, 1973.

(10) Davenport, H. W., "Gastric Mucosal Injury by Fatty and Acetylsalicylic Acids," *Gastroenterology,* 46:245–253, 1964.

(11) Reuter, S. H., and W. W. Montgomery, "Aspirin vs Acetamenophen after Tonsillectomy: A Comparative Double-Blind Study," *Archives of Otolaryngology,* 80:214–217, 1964.

(12) Singer, R., "Acetylsalicylic Acid, A Probable Cause of Secondary Post-Tonsillectomy Hemorrhage," *Archives of Otolaryngolgy,* 42:19–20, 1945.

(13) Fox, S. L., and G. B. West, "Vitamin K and Late Tonsillar Hemorrhage," *Laryngoscope,* 51:564–574, 1947.

(14) Hersh, R. A., "A Clinical Study Comparing the Incidence of Postoperative Bleeding in Patients Using Salicylate-containing Analgesics versus Acetamenophen Analgesics," *Bulletin of the Bergen County Dental Society,* 40:6–8 and 16, 1974.

(15) Speer, F., "Aspirin Allergy: A Clinical Study," *Southern Medical Journal,* 68:314–318, 1975.

(16) Fein, B. T., "Aspirin Shock Associated with Asthma and Nasal Polyps," *Annals of Allergy,* 29:598–601, 1971.

(17) Woodbury, D. M., "Analgesic-Antipyretics, Anti-inflammatory Agents, and Inhibitors of Uric Acid Synthesis: Salicylates and Congeners, Phenacetin and Congeners, Antipyrene and Congeners, Indomethacin, Colchicine, Allopurinol," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 316, 1970.

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

(19) Lim, R. K. S., et al., "Site of Action of Narcotic and Non-narcotic Analgesics Determined by Blocking Bradykinin-Evoked Visceral Pain," *Archives Internationales de Pharmacodynamie et de Therapie,* 152:25–58, 1964.

(20) Scott, D., Jr., "Aspirin: Action on Receptor in the Tooth," *Science,* 161:180–181, 1968.

(21) OTC Volume 130104.

(22) Todd, R. G., "Martindale: The Extra Pharmacopeia," 25th Ed., The Pharmaceutical Press, London, p. 26, 1967.

(23) Davison, C., and H. G. Mandel, "Nonnarcotic Analgesics and Antipyretics I: Salicyclates," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J. R. DiPalma, McGraw-Hill Book Co., New York, p. 383, 1971.

(24) OTC Volume 060008.

(25) Minutes of the Advisory Review Panel on OTC Oral Cavity Drug Products, 27th Meeting, August 14, 1979.

(26) Minutes of the Advisory Review Panel on OTC Oral Cavity Drug Products, 28th Meeting, December 12–14, 1979.

(27) Adriani, J., S. Minokadeh, and M. Naraghi, "Effectiveness on Mucous Membranes of Topically Applied Antipyretic Analgesics," *Regional Anesthesia,* 6:47–50, 1981.

b. *Benzocaine.* The Panel concludes that benzocaine is safe and effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

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

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

Benzocaine has slight antiseptic and bacteriostatic actions, but these actions are not clinically significant. Benzocaine acts, as do other topical anesthetics, on the axonal membrane to interrupt conduction. As is the case with other local anesthetics, it stabilizes the membrane and prevents passage of sodium ions into the axonal cytoplasm, thereby preventing depolarization. Its anesthetic activity is decreased or lost when formulated in an acid medium because it forms salts by the interaction of acids with the amino group (Refs. 1, 2,

and 3). The salts are ionized and do not readily penetrate the lipid barriers of cell membranes. The buffering mechanisms of mucous membranes act to release the basic form. For this reason, the salts are effective on the mucous membranes but not on the intact skin.

(1) *Safety.* The Panel concludes that benzocaine is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzocaine is one of the most widely used and safest topical anesthetics in OTC preparations. In one year 1,300,000 pounds (lbs) were used in the United States for OTC and prescription use. Because it has a low degree of water solubility, the quantities absorbed are relatively insignificant, and plasma levels that cause systemic reactions characteristic of the soluble "caine" type drugs and their allies do not occur with benzocaine. The convulsions and cardiac depression resulting from high plasma levels of the "caine" type drugs do not occur with benzocaine and reports of such reactions with the use of benzocaine are nonexistent. Blood plasma contains pseudocholinesterases which hydrolyze and detoxify esters of aminobenzoic acid, such as procaine, butethamine, and tetracaine. The exact metabolic pathways for the biodegradation of benzocaine in man is not known (Ref. 1). However, it is likely that benzocaine undergoes hydrolysis into aminobenzoic acid and ehtanol. The aminobenzoic acid is converted to aminohippuric acid, or is conjugated with glycine, or is excrete unchanged into the urine.

Benzocaine has been administered orally to relieve stomach pain without any resulting toxic effects. It causes some discomfort by the oral route probably because it forms the hyrochloric salt which is irritating. The lethal dose in man is not known. The Panel is unaware of any fatalities due to oral ingestion of benzocaine. Lethal doses have been determined in animals when benzocaine has been administered by various routes. Astrom and Persson (Ref. 4) determined the toxicity of benzocaine in rabbits and compared it with that of several other soluble topical anesthetics/analgesics of the "caine" type. The anesthetics/analgesics were applied to various mucous surfaces by the intravesicular, intranasal, and intratracheal routes. When administered by the intratracheal route, the LD_{50} (mean lethal dose) for benzocaine was 146 mg/kg (milligrams per kilogram). For tetracaine, it was 4.4 mg/kg. For cocaine, the LD_{50} was 30 mg/kg, and for lidocaine, it was 75 mg/kg. When the drugs were administered intranasally, the LD_{50} for benzocaine was 104 mg/kg, compared to 10 mg/kg for tetracaine, 50 mg/kg for cocaine and 135 mg/kg for lidocaine. Using tetracaine as a reference unit of toxicity and designating this unit as 1, the toxic dosage relationships would be tetracaine 1, cocaine 6.8, lidocaine 17.1, and benzocaine 33.2 when the drugs were administered by the intratracheal route. In other words, approximately 33 times more benzocaine would be required to cause a fatal response than would be required if tetracaine were used. By the intranasal route, the toxic dose relationship is tetracaine 1, cocaine 5, benzocaine 10.4, and lidocaine 13.5. These comparisons indicate that benzocaine is far less toxic than the other compounds tested when administered via the intratracheal and intranasal routes. The data also indicate that when the intranasal route is used, benzocaine is far less toxic than tetracaine and cocaine but slightly more toxic than lidocaine.

Acute lethal dose studies using the oral and intraperitoneal routes of administration in mice also indicate that benzocaine manifests a low degree of toxicity. Zaroslinski (Ref. 5) studied the effects of benzocaine on the cornea of rabbits to determine its potential for producing irritation. The concentrations used ranged from 4 to 20 percent in polyethylene glycol-4,000 dilaureate. Benzocaine caused no detectable irritation of the eyes. He compared benzocaine with the effects of the hydrochlorides of dibucaine, tetracaine, and pramoxine. Dibucaine hydrochloride, 2 percent, and tetracaine hydrochloride, 2 percent, caused irritation consisting of a red, swollen conjunctival sac with copious mucous secretions surrounding the area. This condition persisted in these animals for 48 hours. Pramoxine hydrochloride, 3 to 4 percent, caused extreme swelling and inflammation at the experimental site. The irritation was accompanied by excessive mucous secretion. After 24 hours, the corneal areas became blue in appearance, suggesting blindness.

The systemic effects of benzocaine absorbed percutaneously were also studied by Zaroslinski (Ref. 6). These studies were designed to assess the effects of benzocaine on the hematopoietic system and were conducted in rabbits (Ref. 5). Benzocaine, 20 percent, in a Carbowax™ base was applied to abraded rabbit skin after which blood samples were drawn from a marginal ear vein. Hemoglobin and methemoglobin levels were determined. In addition, erythrocyte, leukocyte, and differential counts were made. The hemoglobin level decreased to the same approximate levels in both the control and experimental animals. Methemoglobin levels increased to less than 3 percent of the total hemoglobin. This response was essentially identical to that occurring in the control and experimental animals. Erythrocyte levels decreased in both the control and experimental animals while the leukocyte count was elevated in both the test and control animals. Differential counts revealed an increase in polymorphonuclear leukocytes and a decrease in lymphocytes in both the control and experimental groups. It was concluded, even though some minor change occurred in each of the parameters studied, that these changes were indistinguishable in the control and experimental groups and that these effects were apparently due to some phenomena other than that of applying the ointment to the abraded skin.

The percutaneous safety of benzocaine was reported by Zaroslinski (Ref. 5) in a study investigating the local effects of repeated application of benzocaine to the abraded skin. The experiment was designed to establish whether or not the use of benzocaine applied repeatedly to the abraded skin of rabbits caused any irritancy or allergenic responses as well as systemic adverse effects. The study was conducted in eight female albino rabbits weighing 2.2 to 3.4 kg. The back of each animal was closely clipped and then abraded in a specific area by repeatedly scraping the skin with the edges of a piece of wire screen, the teeth of which were 1 mm apart. The rabbits were divided into two groups. One group received 5 g ointment twice daily applied to the abraded surface. The second group served as a control, and no ointment was applied. Blood samples were drawn from the marginal ear vein of each animal before and after abrading and tested for the hemoglobin-methemoglobin content, changes in erythrocytes, leukocyte counts, and differential counts. The areas of the abrasion were varied, i.e., they were 3, 6, and 12 square inches, respectively. In all instances the quantity of ointment applied was constant, i.e., 5 g. The weighed amount of ointment was spread uniformly over the abraded areas. The skin was then manipulated by rubbing to cause absorption of the ointment. The entire trunk of each rabbit was protected by a light, muslin bandage.

The drug was applied twice daily, 5 days weekly over a period of 20 days. During this time 200 g of the ointment was applied to the abraded skin area of each of the rabbits. No observable local irritation or signs of allergic reaction were noted nor were there any demonstrable systemic effects as judged by observations of the hematological parameters. During this period, each test animal was inuncted with approximately 80 g/kg ointment. The variations observed in the hemoglobin and methemoglobin values were similar in both the control and the experimental animals.

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

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

As is the case with other drugs, benzocaine can act as a hapten and combine with proteins to cause a sensitivity mediated by IgE immune globulin type of antibodies. These antibodies act on mast cells basophils, and other cells in susceptible individuals and cause anaphylaxis (allergic reactions), rhinitis (nasal inflammation), intrinsic asthma, urticaria (hives), and atopic dermatitis. Benzocaine can also activate the thymus-lymphoid system and cause local sensitization of the cytotoxic type in the skin after repeated applications. The mechanism for development of sensitization is described elsewhere in this document. (See part II. paragraph E. above—Adverse Reactions.)

Fisher, Pelzig, and Kanof (Ref. 7) studied the ability of paraphenylenediamine, a hair dye, to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. They found that in a group of 50 high-risk patients, 2 patients had positive patch reactions to paraphenylenediamine and that 18 patients were also found to be sensitive to benzocaine. They also found that of 24 patients sensitive to benzocaine, 10 were also sensitive to paraphenylenediamine. In a similar study, Gaul (Ref. 8) using a patch test found that in a group of 580 dermatologic patients, 50 were sensitive to paraphenylenediamine and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, three were sensitive to benzocaine only and three were sensitive to paraphenylenediamine, procaine, and benzocaine. Patients showing sensitivity to a variety of substances were characterized as having "cross-sensitivity," "cross-and multiple-sensitivity," and "multiple-sensitivity without cross-sensitivity." The Panel emphasizes that benzocaine is chemically dissimilar to paraphenylenediamine. Since benzocaine can act as a hapten and combine with a tissue protein to form strong covalent bonds to act as an allergen, these findings are not surprising to the Panel.

In the North American Dermatologic Study (Ref. 9), the incidence of benzocaine irritancy and sensitivity was less than 5 percent and equal with other commonly used drugs and less than the more frequent sensitizers, such as neomycin. These studies were performed on high-risk allergic patients seeking treatment for dermatologic diseases. Benzocaine has often been referred to as a potent sensitizer and has been said to cause sensitization and cross-sensitization to other derivatives of aminobenzoic acid, such as procaine, butamben, butethamine, tetracaine, and related compounds. The number of reported reactions that have occurred has not been correlated with the total number of applications of the agent to individual subjects, with repeated applications, and with subjects who are not high risk (Ref. 10). Cross-sensitivity is defined as the capacity of an antibody to react not only with the antigen responsible for its production but also with other antigens that are closely allied chemically. Mathieu (Ref. 11), in reviewing the liteature on cross-sensitivity, found instances of cross-sensitivity among all the local anesthetics to be rare, irrespective of the mode of the administration.

The Panel concludes that the available epidemiologic data on allergy, irritancy, and other reactions are inconclusive and in no way support the contention that benzocaine is a "potent sensitizer." The number of adverse reactions is relatively small when one considers that benzocaine has been used since the early 1900's and has enjoyed wide marketing experience with few complaints. It has been and still is one of the most widely used and safest topical anesthetics in OTC preparations (Refs. 6, 12, and 13). The Panel also feels that such depictions as "potent sensitizers," "common cross-sensitizers," and "highly allergic," imply that these phenomena occur with greater frequency with benzocaine than with other drugs and that such statements are unwarranted. The Panel finds little or no evidence of controlled, investigative, or epidemiological studies to support these contentions. Calnan et al. (Ref. 14) evaluated sensitivity of various allergens by patch tests in 281 housewives exhibiting hand dermatitis in an effort to identify the offending allergen. Only 5 percent of these patents proved to be sensitive to benzocaine. Substances occurring in household items or in chemicals such as balsms, nickel, and rubber were more common allergens than was benzocaine. Bandmann et al. (Ref. 15) in their reevaluation of some of the same data originally reported by Calnan et al. (Ref. 14) showed that the incidence of positive patch tests with benzocaine in male and female patients with allergic dermatitis was 3.3 percent and 4.5 percent, respectively. In view of the fact that only a fraction of the population exhibits any allergic dermatitis, and in view of the fact that these tests were done on high-risk populations, the Panel is of the opinion that the incidence of benzocaine sensitivity is quite low.

One death due to anaphylactic shock immediately following the administration of throat lozenges containing 10 mg benzocaine, 1 mg tyrothricin, and chlorophyll was reported by Hesch (Ref. 16). Circumstantial evidence cited by the author suggests that the death was drug related. However, it was impossible to state which of the components in the lozenge was the causative agent. The Panel is unaware of any similar cases of

anaphylaxis that could be attributable to benzocaine or benzocaine-containing products and concludes that even though benzocaine can act as a hapten and induce an IgE-mediated anaphylactic response, particularly on damaged skin and mucous membranes, the occurrence of anaphylaxis is extremely rare. The use of a 20-percent benzocaine ointment in 132 patients suffering from 22 types of dermatologic conditions was documented by White and Modura (Ref. 17). Included among these were 10 cases of infantile eczema, both dry and weeping, and 10 cases of varicose ulcers. Of the 132 cases, the relief obtained with benzocaine was inadequate in only 2 cases of atopic dermatitis and in 2 cases of lichen simplex chronicus. There were no cases of irritation or sensitivity reactions directly attributable to benzocaine. However, there were 2 cases of aggravation of dermatitis venenata (poison ivy) but not of the atopic dermatitis. Thus, relief due to benzocaine was adequate to excellent in 126 out of 132 patients. The incidence of side effects was 2 out of 132 patients, and these were not of a serious nature. This type of study in a population selected on the basis of dermatologic disease rather than on the basis of the history of drug allergy, tends to provide a better estimate of the incidence of sensitivity in the general population.

Adriani and Campbell (Ref. 18) in a study of the absorption of tetracaine applied on the mucous membranes in various areas of the body comment that the systemic absorption of benzocaine is poor even though benzocaine was not included in this study. They attribute the absence of untoward reactions in 10,000 patients treated with 20-percent benzocaine ointment as a lubricant anesthetic for deadening of pharyngeal and tracheal reflexes during the introduction of endotracheal tubes to this lack of significant absorption. Adriani and Zepernick (Ref. 19) reported a total lack of adverse reactions in over 144,000 cases in which 20 percent benzocaine was used in hospitalized patients. The majority of these cases involved single applications for the lubrication of endotracheal tubes, oropharyngeal airways, and other instruments used in the pharynx and trachea during clinical anesthesia. The studies were performed at the Charity Hospital, New Orleans. Since that time there has been a continued use of benzocaine for the same purpose, and it is estimated that the number of usages since their report was published is an additional 200,000, all without any adverse or allergic reaction.

Prystowsky et al. (Ref. 20) did a perspective contact sensitivity study on 1,158 adult volunteers. A pretest history of previous exposure to four allergens, including 5-percent benzocaine in petrolatum, was obtained before patch testing. The patch was removed at 48 hours and read at 5 days. The prevalance of positive reactions to 5-percent benzocaine was 0.17 percent. By history, 85 percent of the volunteers had been exposed to benzocaine. The investigators point out that the 0.17-percent positive reactions to benzocaine in a study of 127 patients referred to clinics for the evaluation of contact dermatitis. They concluded that "the results of this study indicate that contact dermatitis patient populations provide exaggerated estimates of the prevalence of sensitivity to contactants; figures in a general population are preferable in decisionmaking concerning the safety of commercial products."

Methemoglobinemia has been reported following the topical application of benzocaine on both the skin and the mucous membranes. However, this is an uncommon occurrence. It has been reported to have occurred in subjects less than 1 year of age more often than in adults, but it can occur at any age (Ref. 3). Isolated reports of cases of methemoglobinemia, generally in infants following the use of benzocaine-containing products, have appeared in the literature since 1949. Haggerty (Ref. 21) reported a case of a 1-month-old infant who became cyanotic after a weeping diaper rash was treated with an ointment containing 3 percent benzocaine, 1 percent methapyrilene hydrochloride, calamine, zinc oxide, and camphor. The diagnosis of methemoglobinemia was made by spectroscopic examination of the blood. The condition was reversed with methylene blue. Goluboff and MacFadyen (Ref. 22) reported a case of methemoglobinemia in a 3-month-old patient treated for severe eczema and pruritus with several products. One of these products contained salicylic acid, colloidal sulfur, and coal tar; another product contained 1 percent hydrocortisone in an ointment base; and one product contained 1.5 percent crude coal tar, 7.5 percent titanium dioxide, 7.5 percent zinc oxide, 2.5 percent calamine, 1 percent cetyltrimethyl ammonium bromide, and 5 percent benzocaine in a special water-soluble base. In addition the patient received intramuscular terramycin and oral elixir of phenobarbital. Treatment with methylene blue successfully reversed the methemoglobinemia. Determination of the causative agent was impossible due to the multiplicity of ingredients in the preparation.

Other isolated cases of a similar nature have been reported, but the Panel feels little would be added to understanding the nature of this reaction if these cases were reported in detail. Although most reported cases of methemoglobinemia following topical use of benzocaine have occurred in infants, cases have also been reported involving older children and adults. Bloch (Ref. 23) reported a case in a 6-year-old child, and Bernstein (Ref. 24) reported three cases in adults. Hughes (Ref. 25) suggested that the susceptibility might be due to a deficiency of DPNH-dependent methemoglobin reductase, resulting in a diminished capacity to physiologically protect against methemoglobin-inducing foreign compounds. The experiences recorded by Bloch (Ref. 23) in a 6-year-old child suggest that a far less severe methemoglobinemia occurs in older children than in infants. The reactions in the three adults reported by Bernstein (Ref. 21) suggest that the reactions were of a mild nature. He found that definitive therapy was unnecessary. The reductase in the red blood cells converts the iron in methemoglobin (ferrihemoglobin) from the ferric to the ferrous state. The reconversion of methemoglobin to reduced hemoglobin that is constantly occurring does not take place and an accumulation of methemoglobin results when the enzyme is inhibited by the presence of certain drugs. The methemoglobin imparts a bluish color (cyanosis) to the skin of white and lightly pigmented individuals. In Black and heavily pigmented subjects, the cyanosis can be detected in the nailbeds or in the mucous membranes. The rapidity of development of the bluish color depends upon the rate and amount of benzocaine absorbed. In some cases, it develops within 30 minutes to 1 hour after application. Methemoglobinemia due to benzocaine is not life-threatening because only small amounts are absorbed, particularly after a single application of benzocaine. The cyanosis appears when 2 g or more of hemoglobin have been converted to methemoglobin which is incapable of carrying oxygen. In most cases of methemoglobinemia, the oxygen capacity is not signifcantly decreased. Infants under 1 year of age who have not as yet developed sufficient quantities of the reductase allegedly develop methemoglobinemia more easily than older children and adults, but this point has not actually been verified and clarified in the medical literature. On rare occasions,

older children or adults are found who have a congenital deficiency of the enzyme.

Steinberg and Zepernick (Ref. 26) reported a case of methemoglobinemia during anesthesia which occurred in a 38-month-old Black male at Charity Hospital in New Orleans. The child had been anesthetized with cyclopropane on two previous occasions. On the first occasion, anesthesia was uneventful. On the second occasion, induction of anesthesia was followed by the development of cyanosis which was detected by observing the nailbeds. Anesthesia was discontinued; the operation was deferred until a week later. On the third occasion, anestheis was inducted in the usual manner with cyclopropane and the patient intubated. Cyanosis developed within 15 minutes and anesthesia was discontinued. He remained cyanotic even though he was awake and receiving 100 percent oxygen. There was no change in pulse or blood pressure. Within 4 hours, he regained his normal color and had no apparent ill effects from the experience. A review of the anesthetic records revealed that anesthesia in the first instance, when anesthesia was uneventful, was conducted by using an endotracheal tube that had been lubricated with petrolatum. On the second and third occasions, the endotracheal tube had been lubricated with an ointment containing 20 percent benzocaine in propylene glycol.

The child was studied further by Adriani and Zepernick (Ref. 27). Reapplication of 20 percent benzocaine to the mucous membranes of the mouth and on the tongue promptly produced cyanosis without respiratory distress and without changes in pulse and blood pressure which one would anticipate had suboxygenation been the causative factor. Blood drawn at this time was the color of chocolate. When analyzed spectroscopically, the absorption spectrum was characteristic of that produced by methemoglobin. The cyanosis cleared promptly following the intravenous administration of 1 mg/kg methylene blue in a 1-percent solution. On subsequent days, various drugs were applied to the mucous membranes and the blood analyzed for methemoglobin. Since benzocaine is chemically allied to procaine, the latter being the diethylaminoethanol ester of aminobenzoic acid, procaine was applied to the mucous membranes and the blood analyzed for the presence of methemoglobin. None was found. A saturated aqueous solution of aminobenzoic acid was likewise applied on the mucous membranes with no resultant cyanosis or evidence of methemoglobinemia. A paste consisting of propylene glycol and butamben was likewise applied without any development of methemoglobinemia. Since ethyl alcohol is used to esterify aminobenzoic acid to form benzocaine, it also was applied to determine whether or not there was cross-sensitization with the components of benzocaine. Alcohol, also, did not produce cyanosis nor did the blood show any increase in methemoglobin. The results following the use of 1 percent lidocaine hydrochloride on the mucous membranes were also negative. Propylene glycol applied to the mucous membranes also caused no methemoglobinemia. It appears obvious from these studies that the formation of the methemoglobin was due to the ethyl ester alone and that there was no cross-reactivity between aminobenzoic acid or any of its derivatives.

The majority of the reports that the Panel has reviewed concerning the formation of methemoglobinemia following the use of benzocaine are single, isolated cases of one, two, or three occurrences. It is difficult to extrapolate from these isolated cases with what incidence methemoglobinemia might occur in the general population since the occurrences have not been in any was correlated with the total number of drug applications. Adriani and Zepernick (Ref. 19) reported no cases of sensitivity nor any other adverse reactions in over 144,000 cases after the use of a preparation containing 20 percent benzocaine for lubrication of endotracheal tubes and airways in hospitalized patients. Of these 144,000 cases, there was only 1 occurrence of methemoglobinemia following the application of the benzocaine ointment as a lubricant (Ref. 27).

Methemoglobinemia is not life threatening, particularly when caused by the small amounts of benzocaine absorbed percutaneously or from the mucous membranes following a single application. Methemoglobin is also known as ferrihemoglobin and is incapable of carrying oxygen since the iron has been converted from the ferrous to the ferric state. Cyanosis becomes apparent when 10 to 15 percent of the total hemoglobin has been converted. Methemoglobinemia becomes symptomatic when 30 to 45 percent methemoglobin levels are attained if acutely induced. The symptoms are fatigue, dyspnea, weakness, tachycardia, and headache, and are due to hypoxia produced by the lowered oxygen capacity of the blood. Normally, there is an equilibrium between the concentration of ferrous and ferric components of iron in the hemoglobin. Normally, not more than 1 percent of the iron is in the ferric state. When iron is converted to the reduced state, it can carry oxygen if the globin is not altered. If the globin is altered, cathemoglobin forms. Cathemoglobin is incapable of carrying oxygen even though the iron is reduced to the ferrous state.

There are at least three recognized enzymatic processes which tend to keep the heme moiety of hemoglobin in the ferrous state and reduce the iron to the ferric state as rapidly as the ferrihemoglobin forms. The first mechanism employs an electron donor, nicotinamide adenine dinucleotide ($NAHDH_2$), which is formed from the oxidation of glucose and reduces the ferric heme to the ferrous state in the presence of the enzyme metheglobin reductase. This pathway is the most important of the three and accounts for 67 percent of the conversion of the ferric iron to the ferrous state in red blood cells.

The second pathway by which reduction of methemoglobin is accomplished involves the generation of nicotinamide adenine dinucleotide phosphate ($NADPH_2$) formed in a pentose pathway. In this reaction, methemoglobin can act as a cofactor that facilitates and accelerates the reaction. This pathway accounts for only 55 percent of the reduction of the iron in the red blood cells from the ferric to the ferrous state. The third mechanism involves a glutathione pathway. $NADPH_2$ in the presence of glutathione reductase (GR) reduces the oxidized glutathione to reduced glutathione. The reduced glutathione in the presence of glutathione peroxidase is capable of destroying oxidant compounds capable of oxidizing hemoglobin. This pathway accounts for 12 percent of the methemoglobin converted to normal hemoglobin. Ascorbic acid is a reducing agent and can also be involved in the conversion. It reduces 16 percent of the methemoglobin; however, this is a nonenzymatic process.

The etiologic factors which alter equilibrium between ferrous and ferric iron can be classed into primary and secondary factors. Primary factors are hereditary. In the hereditary states, methemoglobinemia is due to a deficiency of $NAHDA_2$-dependent methemoglobin reductase and hereditary methemoglobinemia with an abnormal hemoglobin. These conditions are rare. The secondary factors are oxidant drugs.

Concentrations of methemoglobin not exceeding 8 percent of the total hemoglobin are normally present without cyanosis. Cyanosis, as stated above, becomes apparent when the methemoglobin level exceeds 10 to 15 percent of the total circulating hemoglobin; however, levels up to 30 percent of the total hemoglobin may produce cyanosis, but not necessarily any clinical symptoms. Methemoglobinemia becomes symptomatic when 30 to 45 percent of the total hemoglobin is oxidized to methemoglobin.

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

Benzocaine differs from the drugs and chemicals, such as acetanilia, sulfanilamide, the aniline dyes, and the nitrites. These latter drugs and chemicals cause methemoglobin to form at a more rapid rate than can be reduced by the enzyme, even though the enzyme is present in adequate quantities in the red cell.

(2) *Effectiveness.* The Panel concludes that benzocaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzocaine is an effective topical anesthetic/analgesic on the skin and mucous membranes. There are many reports in the medical literature of its long, continued, successful use as an anesthetic and an antipruritic in the form of ointments, lotions, sprays, lozenges, and dusting powders that attest to its effectiveness (Refs. 3, 12, 19, and 29). These studies, however, are subjective and uncontrolled. Benzocaine is not suitable for infiltration or perineural injection. When properly formulated with ingredients that insure its stability and continuous contact with a cutaneous or mucous surface it provides prolonged anesthesia (Ref. 12). When incorporated in a medium that is sufficiently alkaline to release bioactive quantities of the free base it penetrates both the intact and damaged skin (Ref. 12). Percutaneous absorption and absorption from the mucous membranes occur, but the resulting blood levels are insignificant. Its pain-relieving action is entirely within the skin or mucous membranes. The quantity circulating in the blood is insufficient to provide anesthesia to parts of the body distant from the site of application.

Since the introduction of newer and more suitable solvents, such as the glycols, there has been a renewed interest in the use of benzocaine as a topical anesthetic/analgesic because of greater effectiveness of preparations formulated with these solvents compared to the oleaginous basis and dusting powders used heretofore. The concentration of benzocaine in the tissue fluids that is bioactive is insufficient to penetrate large nerve trunks. The effect of benzocaine is entirely at the terminal pain receptors in the mucous membranes.

Benzocaine is an effective topical anesthetic/analgesic on the mucous membranes. It as a short latent period on the mucous membranes of the mouth ranging from 30 seconds to 1 minute. The duration of action varies with the duration of contact. A single application of a solution that is diluted with saliva in the mouth and washed away produces anesthesia of 5 or 10 minutes duration. Continuous contact of a benzocaine-containing preparation will produce anesthetic/analgesic for as long as the drug is present in sufficient concentration at the particular test site. The minimum effective concentration to produce anesthetic/analgesic associated with numbness is 5 percent in propylene glycol. There is little to be gained in exceeding a 20-percent concentration. Adriani and Zepernick (Ref. 19) studied the effects of 40 topical anesthetics used the mucous membranes. They found that although benzocaine was effective it ranked low on the list as far as duration of action is concerned. The most effective drugs were tetracaine, cocaine, lidocaine, dyclonine, and dibucaine. These ingredients, however, are readily absorbed and are capable of producing systemic toxicity.

Benzocaine is safe because of its low water solubility; even though concentrations of 20 percent may be applied in a solvent, such as propylene glycol, the amount that dissolves in the tissue fluids remains the same. The solvent merely increases the concentration so that saturated solutions can be made which are bioactive and will pass into the nerve cells. Concentrations less than 5 percent produce the partial blockade which the Panel has termed "analgesia." Various preparations are available in the form of lozenges and rinses containing benzocaine in concentrations less than 5 percent. These are claimed to be effective for the relief of minor pain in the mouth and in the throat, and to provide temporary relief for a sore throat, ulcer pains, and other afflictions of the oral and pharyngeal mucous membranes. Topical anesthetics/analgesics do not penetrate into the deepest or submucosal structures of the mucous membranes and produce anesthesia/analgesia. They are only effective for surface anesthesia/analgesia.

Preparations designed to relieve sore throat generally consist of sugar-containing lozenges having concentrations of benzocaine from 0.1 to 5 percent. The benzocaine is slowly released and coats the mucosa providing partial anesthesia and temporary relief for sore mouth and throat. The recommended dose under these circumstances does not produce numbness and complete loss of reflex activity. There are those who feel that such a degree of pain relief as would be obtained by using concentrations that produce numbness would interfere with the gag reflex and favor the aspiration of mucus or other material which would be swallowed. On the other hand, it is well known that subjects without gag reflex have no difficult in swallowing. The act of swallowing is not interfered with by cocainization of the pharynx as Doty and Bosma (Ref. 30) were able to demonstrate. Loch et al. (Ref. 31) have confirmed these findings. Freystadtl and Morelli (Ref. 32) have shown that the sensation of touch is still preserved after the sensation of pain has been abolished, which explains the lack of problems. The Panel is unaware of any such accidents occurring with concentrations used in OTC preparations. Benzocaine used in the mouth is swallowed but causes no

systemic toxicity. It has been shown that it is safe in concentrations in solutions of glycols up to 20 percent when applied to oral and pharyngeal mucous membranes. Systemic aborption is so slight that blood levels are barely detectable. Furthermore, blood levels are insufficient to produce adverse reactions such as convulsions or cardiac depression, characteristic of the more soluble local anesthetics. It is the consensus of the Panel that 0.1 to 5 percent concentrations may be used for anesthesia in the form of rinses. Two to 15 mg may be incorporated in lozenges that allow the slow release of the product and continuous bathing of the affected area with a dilute concentration of the benzocaine. The action from sprays, rinses, and gargles is relatively short, since the duration of contact is not early so long as it would be from the slow release from a lozenge. Pain due to ulcers, inflammation of the mucous membranes, etc., may be relieved by using sprays and rinses or swabbing the affected area. The relief is of short duration, usually less than 30 minutes, but in some individuals it may persist for a longer time.

Benzocaine does not penetrate the mucous membranes of the gingiva to relieve pain in the gingiva, tooth, or other types of pain arising in submucosal structures. Benzocaine does not penetrate the mucous membranes into the muscles of the pharynx, tongue, and other structures of the oral cavity. The Panel, therefore, recommends that the labeling for benzocaine-containing products for use in the oral cavity be limited to claims for the relief of soreness or irritation or minor pains of the mucous membranes of the mouth and throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 20.0-percent concentration of benzocaine in the form of a gel or spray not more than three to four times daily. Use a 0.05- to 0.1-percent concentration of benzocaine in the form of a lozenge (equivalent to 2.0 to 15.0 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

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

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

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

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

(5) OTC Volume 060073.

(6) OTC Volume 060087.

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

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

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

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

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

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

(13) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 186–187, 1973.

(14) Calnan, c. D., et al., "Hand Dermatitis in Housewives," *The British Journal of Dermatology,* 82:543–548, 1970.

(15) Bandmann, H. J., et al. "Dermatitis from Applied Medicaments," *Archives of Dermatology,* 106:335–337, 1972.

(16) Hesch, D. J., "Anaphylactic Death from Use of a Throat Lozenge," *Journal of the American Medical Association,* 172:62–65, 1960.

(17) White, C. J., and J. W. Madura, "Topical Anesthesia in Dermatology," *Postgraduate Medicine,* 9:519–520, 1951.

(18) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

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

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

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

(22) Goluboff, N., and D. J. MacFadyen, "Methemoglobinemia in an Infant: Associated with Application of a Tar-Benzocaine Ointment," *The Journal of Pediatrics,* 47:222–226, 1955.

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

(24) Bernstein, B. M., "Cyanosis Following Use of Anesthesin (Ethyl-Amino-Benzoate)," *The Review of Gastroenterology,* 19:411–412, 1952.

(25) Hughes, J. R., "Infantile Methemoglobinemia Due to Benzocaine Suppository," *Journal of Pediatrics,* 66:797–799, 1965.

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

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

(28) Rao, V. K., et al., "Methemoglobinemia Following the Use of Topical Local Anesthetics," *in* "ASA Annual Meeting Abstracts of Scientific Papers," American Society of Anesthesiologists, Park Ridge, IL, pp. 183–184, 1978.

(29) Adriani, J., and H. Dalili, "Penetration of Local Anesthetics Through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–840, 1971.

(30) Doty, R. W., and J. F. Bosma, "An Electromyographic Analysis of Reflex Deglutition," *Journal of Neurophysiology,* 19:44–60, 1956.

(31) Minutes of the Advisory Review Panel on OTC Oral Cavity Drug Products, 27th Meeting, August 14, 1979, and 28th Meeting, December 12, 13, and 14, 1979.

(32) Freystadtl, B., and G. Morelli, "Sensibililatsprufungen and der Zunge. Beitrag zur Physiologie der sensiblen Nerven," *Beitrage Anatomie, Physiologie, Pathologie, und Therapie des Ohres,* 22:344–371, 1925.

c. *Benzyl alcohol.* The Panel concludes that benzyl alcohol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol is one of the alcoholic or hydroxy-type of topical anesthetics. Benzyl alcohol is phenyl methanol. It may also be looked upon as methyl alcohol with a phenyl group replacing one of its hydrogen atoms. It is also known as phenmethylol hydroxy toluene. It is found in nature in a free state in oil of jasmine (6 percent) and in the form of esters in Peru balsam, tolu balsam, and storax. The commercial product is synthetic, made by

hydrolyzing benzyl chloride or by reducing benzaldehyde. Benzyl alcohol is a colorless liquid with a faint aromatic odor. It has a sharp burning taste and boils at 206° C. It has a specific gravity of 1.042 to 1.047. One gram dissolves in approximately 30 g water making a solution of approximately 4 percent concentration. Aqueous solutions are neutral. Solutions may be sterilized by boiling. Benzyl alcohol is soluble in alcohol (1 g dissolves in 1.5 mL alcohol) and is soluble in ether and chloroform. It dissolves in vegetable oils. Oxidation converts it to benzaldehyde. Slow oxidation occurs if it is exposed to the air for days or weeks. It is stable in stoppered containers (Refs 1 and 2).

(1) *Safety.* The Panel concludes that benzyl alcohol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol is relatively nontoxic. It has been used orally as an antispasmodic agent and rectally as a topical anesthetic/analgesic. It has been used rectally in combination with paraldehyde to anesthetize the mucosa and prevent expulsion of the drug. Benzyl alcohol is converted to hippuric acid in the body and this metabolite is excreted into the urine (Ref. 3).

The effect of large doses of benzyl alcohol was studied in animals by Macht (Ref. 4). The minimum lethal dose of pure benzyl alcohol in white mice is 1 mL/kg. The minimum lethal dose in rats ranged from 1 to 3 mL/kg. In dogs, 2 mL/kg of benzyl alcohol injected intravenously, peritoneally, subcutaneously, and intramuscularly was never fatal. Convulsions and caridiac depression, characteristic of the "caine" type of topical anesthetics, have not occurred when therapeutic or toxic doses of benzyl alcohol have been administered to man or animals. Lethal doses in mice cause respiratory failure and in some cases convulsions. Larger animals, such as dogs, do not manifest these responses. Although benzyl alcohol can, like any other drug, act as a hapten and be antigenic, cases of sensitization have not come to the Panel's attention. The potential for sensitization is lower than it is with the "caine" type of topical anesthetics (Ref. 5).

(2) *Effectiveness.* The Panel concludes that benzyl alcohol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Benzyl alcohol belongs to the hydroxy group of topical anesthetics and differs in chemical behavior from the "caine" type drugs. Benzyl alcohol is lipophilic and penetrates the cells of the mucosa and the axonal membranes of nerve fibers. Aqueous solutions of benzyl alcohol are neutral. It does not form salts. Benzyl alcohol is not ionized, and its penetration into the skin and mucous membranes and pharmacologic activity do not depend upon pH. It blocks transmissions of electrical impulses along sensory and motor nerves. Its mode of action is believed to be similar to the "caine" type of drugs.

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

Benzyl alcohol manifests varying degrees of bacteriostatic and antiseptic activity. However, this antimicrobial effect does not apply to all pathogenic bacteria and reliance cannot be placed upon it. Benzyl alcohol is effective topically in relieving pain and other discomfort due to ulcers, sore throats, and other lesions affecting mucous membranes of the oral cavity. Solutions composed of equal parts of 33 percent benzyl alcohol, water, and ethyl alcohol are effective in relieving itching and burning on the skin (Ref. 2). Ointments consisting of 10 percent banzyl alcohol in large doses have been used for topical application to the skin.

The duration of action of benzyl alcohol in the usual therapeutic doses is brief depending upon the area of application and duration of contact. The latent period on the mucous membranes is approximately 2 minutes. The duration of action of a 1-percent solution on the skin is usually less than 30 minutes. The duration of anesthetic/analgesic action on the mucous membranes is variable, usually depending upon formulation used. The effect is sustained if incorporated in lozenges and lasts as long as the mucous membranes are bathed in sufficient concentrations. The duration of action when the drug is incorporated in rinses is brief, seldom more than 5 or 10 minutes.

The pure alcohol causes smarting and burning initially when applied to the mucous membranes. Although benzyl alcohol is effective as a topical anesthetic/analgesic, Adriani and Zepernick (Ref. 6) found its effectiveness to be less than that of the "caine" type drugs. However, the Panel concludes that benzyl alcohol is safe and effective for use in drops, rinses, mouthwashes, sprays, or in lozenges on the intact mucous membranes of the mouth and throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.05- to 10.0-percent concentration of benzyl alcohol in the form of rinses, mouthwashes, drops, or sprays not more than three to four times daily. Use a 0.05- to 10.0-percent concentration of benzyl alcohol in the form of a lozenge (equivalent to 100 to 500 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

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

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

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

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

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

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

d. *Dyclonine hydrochloride.* The Panel concludes that dyclonine hydrochloride is safe and effective as an OTC

anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Dyclonine is a base which forms a hydrochloride salt. The structure of dyclonine hydrochloride is a modification of the general structural configuration of the commonly used local anesthetics of the "caine" type of drugs, such as lidocaine and tetracaine (Ref. 1). It is a nitrogenous base; however, it is a propiophenone derivative (Ref. 2). One end of the dimethylene chain of the ketone is attached to the nitrogen atom of the piperidine group of the first carbon atom which carries the ketonic group. This is attached directly to a benzene ring which is attached to a butoxy group in the para position. Thus, unlike procaine, lidocaine and other "caine" type drugs, it is neither an amide nor an ester, nor can it be considered an ether, as is the case with pramoxine.

Dyclonine hydrochloride is a white crystalline powder. One gram dissolves in approxiamtely 50 mL water. It is soluble in acetone, alcohol, and chloroform. The crystals melt between 173° and 178° C. It is also soluble in washable cream bases. Its chemical name is 4-n-butoxy-beta piperidino-propiophenone hydrochloride (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that dyclonine hydrochloride is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

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

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

The cardiovascular effects of dyclonine hydrochloride were investigated in dogs anesthetized with sodium barbital (Ref. 6). The drug was administered over a 25-second period within a dose range of 0.25 to 10 mg/kg in 10 dogs. Dyclonine hydrochloride lowered arterial pressure approximately 10 mm Hg (10 millimeters mercury) at a dose of 1 mg/kg. There was a progressive increase in response at doses of 1, 2, 3, 4, and 5 mg/kg with death being produced at a dose of 10 mg/kg. The mechanism of this reduction in blood pressure was found to be due to a decrease in cardiac output as well as to peripheral arterial dilation. Initially, dyclonine hydrochloride induces some respiratory stimulation when administered intravenously to dogs. As the dosage is increased, depression of respiration and oxygen consumption occurs. Dyclonine hydrochloride has been shown to act as an anticonvulsant, acting as a multisynaptic and spinal reflex depressant (Ref. 6).

Chronic toxicity studies were done with dyclonine hydrochloride in the albino rat and in the dog (Ref. 6). Dyclonine hydrochloride did not significantly affect the growth rate of male or female weaning albino rats as compared to controls when it was administered intraperitoneally for 30 consecutive days. A group of 48 rats were studied. They were divided into four groups. Half of the females and half of the males were given the drug and the other half of each were used as controls. Half of the animals were sacrificed and autopsied. No gross pathologic changes were noted in either group. The drug-treated survivors and controls were mated, and the drug-treated group did not differ from the controls in their reproductive capacity. Upon weaning, the offspring of the first group when subjected to the same experiment also did not differ from their controls either as to growth rate or reproductive capacity. No gross pathologic changes were observed in these animals when sacrificed. Experimental observations in dogs, likewise, showed no gross pathologic changes when given doses varying from 5 to 12 mg/kg twice daily, intramuscularly or subcutaneously. No significant changes from normal were noted in hemoglobin concentration, red and white blood cell counts, and differential counts measured at biweekly intervals (Ref. 6).

In human beings, dyclonine hydrochloride possesses a relatively low degree of toxicity. When applied topically to the skin of 3,656 patients in the form of a cream and to 2,000 additional cases in the form of a solution for topical anesthesia, only two cases of proven sensitivity were reported. It was concluded from these studies that the sensitizing potential of dyclonine hydrochloride under conditions of clinical use is low. In a study using a dyclonine hydrochloride solution, no adverse effects were found. Use of concentrated solutions of 2 percent or more have produced irritations and slough of the nasal mucosa in several cases.

In study dealing with the safety of dyclonine hydrochloride following oral administration, 35 patients were given from 300 to 600 mg daily for periods of time varying from 1 to 12 weeks (Ref. 7). No undesirable side effects occurred. It was concluded that the compound would be entirely safe for human consumption. Adriani and Campbell (Ref. 8) emphasized that the two safest anesthetics for use on the mucous membranes for endoscopic procedures are benzocaine and dyclonine hydrochloride. Each shows the least incidence of systemic reactions.

(2) *Effectiveness.* The Panel concludes that dyclonine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Dyclonine hydrochloride is a highly effective anesthetic/analgesic for topical use, particularly on mucous surfaces and on abraded and damaged skin. While it is also an effective nerve-blocking agent, it is irritating if injected and may produce sloughing of tissue. It is, therefore, recommended for topical use only. Dyclonine hydrochloride blocks transmission at nerve endings in the same manner as do other topical anesthetics of the "caine" type of closely related to the "caine" type. The product is marketed as a salt (hydrochloride). Dyclonine hydrochloride is not absorbed through the intact skin in significant quantities to produce anesthesia. It is effective on the mucous membranes. In studies on the mucous membranes conducted by Adriani et al. (Ref. 9), dyclonine hydrochloride ranked fourth in effectiveness, being preceded by dibucaine, cocaine, and tetracaine. One percent dyclonine hydrochloride produced a duration of action of anesthesia of 27 minutes, preceded by a latent period of 2 to 3 minutes. The fact that dyclonine hydrochloride is effective on the mucous membranes is well established. The duration of action of dyclonine hydrochloride as an anesthetic/analgesic is considerably

longer than that of benzocaine, benzyl alcohol, and the phenol type compounds. When used in the form of a rinse or gargle, it may relieve pain in irritated mucous membranes for as long as an hour. When incorporated in lozenges that are slowly sucked, the mucous membranes are bathed continously, and it may relieve pain due to sore throat or sore mouth for several hours or as long as an effective concentration is being supplied by the lozenge.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.05- to 0.10-percent concentration of dyclonine hydrochloride in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a 0.05- to 0.10-percent concentration of dyclonine hydrochloride in the form of a lozenge (equivalent to 1.0 to 3.0 mg per lozenge) every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice or supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

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

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadephia, pp. 466–469, 1973.

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

(4) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 459, 1976.

(5) Abreu, B. E., et al., "Pharmacologic Properties of 4-Alkoxy-B-(1-Piperidyl) Propiophenones," *Journal of Pharmacology and Experimental Therapeutics,* 115:419–426, 1955.

(6) OTC Volume 060025.

(7) Kumperman, H. F., personal communication of July 8, 1955, in OTC Volume 060025.

(8) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

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

e. *Hexylresorcinol.* The Panel concludes that hexylresorcinol is safe and effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hexylresorcinol, an aromatic alcohol, is a dihydroxybenzene with a normal hexyl group on position 4 and hydroxyl groups on positions 1 and 3 of the aromatic nucleus. It can, therefore, be classified as a phenol. It responds to certain specific chemical tests characteristic of phenols. Hexylresorcinol is prepared by condensing resorcinol with caproic acid in the presence of zinc chloride. The resulting intermediate product is reduced to hexylresorcinol (Refs. 1, 2, and 3).

Hexylresorcinol is a white or yellowish-white powder composed of needle-shaped crystals. It has a faint "fatty" odor and a sharp astringent taste. It produces a sensation of numbness when placed on the tongue. Hexylresorcinol melts between 62° and 67° C. It turns from a white to a brownish-pink tint on exposure to light and air due to oxidation to quinones. One gram of hexylresorcinol dissolves in approximately 2,000 mL of water. It is freely soluble in alcohol, glycerine, ether, chloroform, benzene, and vegetable oils. For many years, hexylresorcinol was considered official and was included in the "United States Pharmacopeia."

Animal studies indicate a low degree of acute and chronic toxicity (Ref. 4). In rats, the oral minimum lethal dose of a suspension is 50 mg/kg. A suspension in 5 percent olive oil solution administered subcutaneously resulted in a minimum lethal dose of 750 to 1,000 mg/kg. A similarly low degree of toxicity was found in guinea pigs, rabbits, cats, and dogs. In dogs, doses of 1 to 3 g produced no signs of toxicity. When the dogs were sacrificed, mild irritation of the stomach was noted 4 to 5 hours after ingestion of the drug. Lesions in the mucosa were superficial. If the animals were sacrificed 48 hours later, the lesions were not present. Oral administration in rats was well tolerated, revealing no signs of toxicity when 12 mg/kg was repeated six times over a 8-hour period (Ref. 4).

Pure hexylresorcinol is irritating to the respiratory tract and to the skin. A concentration of hexylresorcinol in alcohol has vesicant properties. Hexylresorcinol lacks the irritancy and caustic properties of resorcinol and phenol. Long use over 40 years and extensive marketing experience indicate that hexylresorcinol possesses a low degree of sensitization.

(1) *Safety.* The Panel concludes that hexylresorcinol is safe as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

In view of the fact that hexylresorcinol was extensively used as an anthelminthic and administered orally in both adults and children, the Panel considers hexylresorcinol to be safe for topical application to the mucous membranes and skin (Ref. 5). The usual adult dose as an anthelmintic is 1 g as a single dose in a 24-hour period. For children, the usual dose is 0.1 g for each year of age up to 10 years. The drug is usually given orally after an overnight fast. The presence of food lessens the effectiveness of the drug. A saline purge is usually given the following morning to clear the bowel of dead worms. Treatment may be repeated after 3 days (Ref. 1). Hexylresorcinol has also been shown to have some antimicrobial effects. The drug has been used as a gargle and as a urinary antiseptic. Experiments by Leonard (Ref. 6) resulted in the use of hexylresorcinol as a urinary antiseptic. He found that hexylresorcinol at pH 6 to 6.4 in a 1:60,000 concentration killed microbes in the urine in 1 hour, and that at pH 7.6 to 8.2 a concentration of 1:18,000 was required for the same effect. Robbins (Ref. 7) observed that after oral administration of hexylresorcinol in humans, 18 percent was eliminated in the urine in a conjugated form, and 64 percent was eliminated in the feces in an uncombined state.

(2) *Effectiveness.* The Panel concludes that hexylresorcinol is effective as an OTC active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hexylresorcinol is a phenol. The substitution of an aliphatic radical on the side chain of this phenol reduces the caustic activity of phenol, but retains the anesthetic qualities of phenol. Thus, the Panel is of the opinion that hexylresorcinol does have anesthetic properties.

Hexylresorcinol solution, 0.1 percent, produces topical anesthesia in the cornea of rabbits lasting up to 10 minutes or more, depending on the concentration of the hexylresorcinol. Hexylresorcinol has been incorporated in lozenges for the relief of sore throat and other painful ailments of the oral cavity.

Adriani and DiLeo (Ref. 8) found that after stimulation by an electric current the application of a commercial preparation consisting of a 1:1,000 solution of hexylresorcinol produced anesthesia on the gums and at the tip of the tongue, but did not completely abolish sensation. The duration of action of aqueous solutions used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 or 10 minutes. When incorporated in lozenges that slowly release the ingredients, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve the pain of sore mouth or sore throat.

The ingredient has also been recommended as an antimicrobial agent for cuts, wounds, and burns on the skin, but the submissions to the Panel do not make this claim (Refs. 9, 10, and 11). The Panel concludes that long usage and wide marketing experience in addition to animal data are adequate evidence for classifying hexylresorcinol as a Category I ingredient for use on the mucous membranes.

(3) *Dosage:* Adults and children 3 years of age and older: Use a 0.05- to 0.1-percent concentration of hexylresorcinol in the form of a rinse, mouthwash, gargle, or spray no more than three to four times daily. Use a lozenge containing 2.0 to 4.0 mg of hexylresorcinol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 582–583, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 618, 1976.

(3) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 644–646, 1955.

(4) OTC Volume 130138.

(5) Brown, E. A., W. Krabek, and R. Skiffington, "A New Antiseptic Solution for Topical Application: Comparative In Vitro Studies," *New England Journal of Medicine,* 234:468–472, 1946.

(6) Leonard, V., "Secretion of Bactericidal Urine and Disinfection of the Urinary Tract Following Oral Administration of Certain Alkyl Derivatives and Resorcinol," *Journal of the American Medical Association,* 83:2005–2012, 1924.

(7) Robbins, B. H., "Quantitative Studies on the Absorption and Excretion of Certain Resorcinols and Cresols in Dogs and Man," *Journal of Pharmacology,* 52:54–60, 1934.

(8) Adriani, J., and J. DiLeo, "The Effectiveness of Hexylresorcinol as a Topical Analgesic on the Mucous Membrane of the Oral Cavity," draft of unpublished paper in OTC Volume 060150.

(9) OTC Volume 130030.

(10) OTC Volume 130031.

(11) OTC Volume 130074.

f. *Menthol.* The Panel concludes that menthol is safe and effective as an OTC anesthetic/analgesic active ingredient for use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Menthol is a secondary alcohol extracted from peppermint oil or made synthetically. Chemically, it is also known as hexahydrothymol and 3-paramenthanol. Menthol exists as colorless hexagonal crystals, as needlelike crystals in fused masses, or as a crystalline powder with a peppermint-like odor. Levo menthol melts between 41° and 44° C. Natural menthol is known as peppermint camphor. It may be levorotatory [1-menthol] or racemic (d,1-menthol). Menthol may be made synthetically by the hydrogenation (reduction) of thymol. Menthol is a secondary alcohol which can be considered to have been derived from the saturated hydrocarbon p-menthanol. Menthol is very slightly soluble in water, but soluble in alcohol, ether, chloroform, mineral oil, and in fixed and volatile oils (Refs. 1 and 2). Menthol may be fatal if ingested in large quantities. Doses of 1 to 2 g/kg may be fatal (Refs. 1 and 3).

(1) *Safety.* The Panel concludes that menthol is safe as an OTC active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Menthol causes sensitization in certain individuals. Symptoms include urticaria, erythema, and other cutaneous lesions. The sensitization index is low, however. Menthol has caused asphyxia in infants when applied locally for the treatment of coryza (runny nose).

Menthol was formerly used internally as a carminative. As the active ingredient of peppermint oil, it has found wide acceptance in candy, chewing gum, and cigarettes (Refs. 4 and 5). Menthol has had extensive use in inhalant preparations for the nose and throat. Inhalers containing menthol are commonly used for the relief of nasal congestion, headache, and neuralgia (Ref. 5).

Toxic effects from excessive ingestion of mentholated products can include nausea, abdominal pain, vomiting, and symptoms of central nervous system depression, such as dizziness, staggering gait, flushed face, sleepiness, slow respiration, and coma. The fatal dose of menthol in man is about 2 g (Refs. 6 and 7). Menthol is excreted in the bile and urine as a glucuronide (Ref. 8).

Rakieten, Rakieten, and Boyd (Ref. 9) studied the effects of menthol vapor on the upper respiratory tract of rats. The rats were exposed to different menthol vapor concentrations over a period of several months. Vapor in a range of less than 0.275 ppm showed no toxic effects, and there were no significant changes in skeletal muscle, skin, brain, or internal organs. Animals did show indications of lung irritation when exposed to the highest menthol concentrations.

In an unpublished study, Thomas (Ref. 10) used an ointment containing several volatile substances, including 2.5 percent menthol. It was applied to the abraded and intact skin of 223 subjects. After 48 hours, no instances of inflammation, wheal, hives, or primary irritation were seen.

Bliss and associates (Ref. 11) studied the effects of a 20-percent oil solution of menthol vigorously applied to the skin. They noted an intense and lasting cooling sensation followed by numbness, with a slight smarting sensation and hyperemia. Irritation beyond the rubefacient stage was not observed. Repeated topical application of mentholated products on the skin has been reported to give rise to hypersensitivity reactions (Refs. 8 and 12).

In young childrem nasal drops containing menthol may bring about spasm of the glottis. Cases of dangerous asphyxiation have been reported in infants following local application of menthol (Ref. 8). However, in a survey of approximately 124,000 infants receiving nasal drops containing essential oils, including menthol, no untoward effects were noted (Refs. 13 and 14).

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

(2) *Effectiveness.* The Panel concludes that menthol is effective as an OTC active ingredient for topical use on the mucous membranes when used within the dosage limit set forth below.

There are few well-controlled studies documenting the effectiveness of menthol as a topical anesthetic/analgesic for use on the mucous

membranes of the mouth and throat. However, due to its wide use and clinical acceptance, and on the basis of published reports in the literature (Refs. 12, 15, and 16), the Panel concludes that menthol is effective for such use.

Menthol belongs in the hydroxy-type group of local anesthetics It stimulates the nerves for the perception of cold and may depress the nerves for pain on the skin and mucous membranes (Ref. 1). In some cases, it merely substitutes one sensation for another.

Menthol is used as an antipruritic on the skin in a concentration range of 0.25 to 1.0 percent (Ref. 2). It also possesses counterirritant properties. When applied to the skin and mucous membranes of the mouth and throat, menthol stimulates the nerves for perception of cold while depressing those nerves which perceive pain.

Menthol is a feeble topical antimicrobial. Menthol is absorbed through the mucous membranes and penetrates the intact as well as the damaged skin. Menthol is indicated for the temporary relief of pain of the mucous membranes of the mouth and throat.

The duration of action of aqueous solutions of menthol used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 to 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.04- to 2.0-percent concentration of menthol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 2.0 to 20.0 mg of menthol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, pp. 697–698, 1973.

(2) "United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 302, 1975.

(3) Seel, H., "Pharmakologische Untersuchungen uber naturliches und synthetisches Menthol," *Archives of Experimental Pathology and Pharmacology,* 122:338–353, 1927.

(4) Claus, E. P., V. E. Tyler, and L. R. Brady, "Pharmacognosy," 6th Ed., Lea and Febiger, Philadelphia, p. 170, 1970.

(5) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 721, 1975.

(6) Arena, J. M., "Poisoning: Chemistry, Symptoms, Treatments," Charles C. Thomas, Springfield, IL, pp. 236–245, 1963.

(7) Deichmann, W. B., and H. W. Gerarde, "Symptomatology and Therapy of Toxicological Emergencies," Academic Press, New York, p. 251, 1964.

(8) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 374, 1972.

(9) Rakeiten, N., M. L. Rakeiten, and M. Boyd, "Effects of Menthol Vapor on the Intact Animal with Special Reference to the Upper Respiratory Tract," *Journal of the American Pharmaceutical Association (Scientific Editiron),* 43:390–392, 1954.

(10) OTC Volume 060298.

(11) Bliss, A. R., and H. B. Glass "A Chemical and Pharmacological Comparison of the Menthols," *Journal of the American Pharmaceutical Association (Scientific Edition),* 29:171–175, 1940.

(12) Rudzki, E., and D. Kleniewska, "Kontaktallergie auf einige Lokaltherapeutika und Konservierungsmittel," *Dermatologica,* 143:36–42, 1971.

(13) Breuninger, H., A. Hildmann, and H. Hildmann, "Zur nasalen Anwendung atherischer Ole im Sauglings- und Kleinkindesalter," *Internationale Zeitschrift fur Vitaminforschung,* 40:800–804, 1970.

(14) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Jounral of the American Medical Association,* 162:1527–1530, 1956.

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

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

g. *Phenol.* The Panel concludes that phenol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenol is hydroxybenzene. Phenol was discovered in 1934 in coal tar by Ringe, who named it "carbolic acid." It was also once called phenic acid (Ref. 1). Phenol is a primary alcohol of the aromatic series and as such exerts a topical anesthetic action (Ref. 2). Although it may be obtained from coal tar, most of it is now prepared synthetically. The antimicrobial effectiveness of phenol was first demonstrated by Lister in 1857. Its clinical use at present is limited to use as a topical anesthetic and for cauterization (Ref. 3). Compounds less toxic than phenol are more effective antimicrobial agents (Ref. 1). Phenol exists as colorless to light-pink, needle-shaped crystals interlaced or separated, or as a white to light-pink crystalline mass (Ref. 4). It possesses an aromatic odor which is distinctive and differs from other aromatic alcohols. It gradually darkens on exposure to light and air. Phenol is liquified by warming or by the addition of 10 percent water. It is caustic if applied directly to tissues (Ref. 1). A concentrated solution of phenol and water has a strength of approximately 6 percent at room temperature. Phenol is very soluble in alcohol, glycerin, chloroform, ether, and fixed and volatile oils (Ref. 4). It is sparingly soluble in mineral oil. Solutions of phenol are oxidized and turn brown due to the formation of quinones (Ref. 1). Phenol forms a salt, phenolate sodium, with sodium hydroxide which is ionized and highly alkaline. One gram dissolves in about 5 mL of water. Phenol boils at about 182° C. It congeals at temperatures lower than 39° C. Phenol combines with camphor to form a substance known as camphor-phenol (Ref. 5). Whether or not this is a definite chemical complex or a solution of phenol in camphor has not been established with certainty, but the consensus seems to be that it is a complex. The substance releases free phenol slowly in small quantities. The presence of moisture hastens the process (Ref. 1).

(1) *Safety.* The Panel concludes that phenol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Concentrations greater than 1.5 percent in aqueous solutions are irritating and may cause sloughing and necrosis (Refs. 3 and 8). Phenol causes an area of blanching when applied in pure form to the skin or mucous membranes. A feeling of numbness develops. Later the area undergoes necrosis and sloughing (Ref. 1).

After oral ingestion or absorption from other sites from which it may pass into the systemic circulation, phenol is oxidized and conjugated with sulfuric, glucuronic, and other acids by the liver and excreted into the urine. Only small quantities of free phenol are excreted into the urine. Phenol is lipophilic and is readily absorbed through the intact and damaged skin and passes into the systemic circulation (Ref. 7). Absorption through the skin depends upon the area exposed rather than on the concentration (Refs. 3 and 8).

Phenol is readily absorbed after application to the mucous membranes. Concentrated solutions are toxic and cause death if ingested orally (Ref. 8). Phenol has been used for suicidal purposes. Cases of accidental poisoning have been common. The symptoms of toxicity usually develop rapidly and death has occurred within 2 or 4 hours after ingestion. Coma and collapse are the main manifestations of toxicity from large doses. After ingestion of small amounts, the most common symptoms are nausea, vomiting, collapse, pallor, cold sweats, and feeble pulse. Stupor ensues deepening into a comatose state with insensibility. Respirations are often rapid and shallow, irregular, and sometimes paroxysmal. Death results from respiratory arrest. Paralysis of both sensation and motion may occur. In some cases, violent clonic or epileptiform convulsions have occurred. The urine is generally scanty, albuminous, and greenish or black in color. The diagnosis is usually not difficult to make, since the odor of phenol can be detected on the breath and smelled in the smoky urine. White, corrugated spots are present on the mucous membranes of the mouth and throat due to the caustic action of the phenol.

The estimated fatal dose of phenol is approximately 15 g. However, death has been reported following the ingestion of as little as 1.5 g. Recovery has followed the ingestion of as much as 30 g. In the fatal cases, death usually occurs in less than 2 hours. Death usually occurs from respiratory failure, although in some instances cardiac failure has been the lethal terminal manifestation. The degree of toxicity depends upon the amount of phenol ingested. Its concentration is not an important consideration (Refs. 1 and 8). Chronic ingestion of phenol causes a dark brown discoloration of tissues most likely due to staining from quinones resulting from oxidation of phenol in the body. The cartilaginous tissues of the body appear to be affected more than other tissues (ochronosis).

(2) *Effectiveness.* The Panel concludes that phenol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenol penetrates the sensory nerve endings and exerts its anesthetic effect in presumably the same manner as other local anesthetics/analgesics (Refs. 6 and 7). It is a lipophilic non-ionized polar substance and thought to act in the same manner as the "caine" type of topical anesthetics (Ref. 9). The hydrocarbon pole is lipophilic and orients into the lipid phase of the axon. The hydroxyl group is hydrophilic and orients into the water phase (Ref. 10). Phenol is acidic and forms salts with alkalis. It readily traverses epithelial barriers. Its absorption from the skin and mucous membranes does not depend upon the pH of the medium. A feeling of warmth and tingling ensues following the application of 5 percent phenol to the unabraded skin. Eventually, complete topical anesthesia/analgesia develops and the area becomes irritated. Phenol can, in concentrations exceeding 1.5 percent in water, be very irritating, and even caustic to the skin and mucous membranes and cause necrosis. Phenol possesses topical anesthetic/analgesic activity in concentrations of 0.5 to 1.5 percent. The blockade produced on the mucous membranes in concentrations of less than 1.5 percent is reversible. The latent period is short, being 1 to 2 minutes. Duration of anesthesia/analgesia on the mucous membranes of the mouth averages 5 to 10 minutes when used in the form of an aqueous solution as rinses, mouthwashes, and gargles. When incorporated in lozenges which slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat. As the drug is washed away by the saliva, the anesthetic/analgesia action recedes.

Duration of anesthesia/analgesia depends upon the site of application and concentration. Aqueous solutions stronger than 2 percent are too irritating for topical application. A 4-percent solution in glycerin is sometimes used and is said to be noncaustic. Because the glycerin helps retain the phenol when camphor is added to phenol, a liquid forms. Phenol forms a complex with camphor and holds it, releasing it slowly. Its rate of release depends upon the quantity of moisture present on the surface of application, temperature, and other factors. The quantity of phenol release from the mixture varies and depends upon the water content of the tissue. This apparently reduces the extent of the topical action and the absorption of phenol through its phenol-holding property (Ref. 5). The Panel questions the safety of such mixtures. Phenol is a keratolytic, neurolytic, and destructive agent in concentrations of 10 to 40 percent (Ref. 1).

Phenol is an anesthetic/analgesic to the mucous membranes. A 5–percent solution of phenol and water has definite topical anesthetic/analgesic action, but sloughing occurs in about 10 percent of the cases (Ref. 11).

A 5–percent solution of phenol in 95 percent alcohol is an efficient topical anesthetic/analgesic. Complete anesthesia results in 53 percent of the cases and partial anesthesia/analgesia in 47 percent of the cases.

However, sloughing or superficial necrosis occurred in 22 percent of cases studied. Phenol is soluble in oils and petrolatum which tend to hold it in solution and reduce its activity.

When phenol is combined with topical anesthetics/analgesics of the nitrogenous type which are active in the basic form, conversion of the nitrogenous base to the acid form occurs because phenol is an acid. This may nullify their action and not necessarily produce the anticipated effect or summation. The antimicrobial activity of phenol is due to its ability to coagulate proteins.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 0.5- to 1.5-percent concentration of phenol in aqueous solution in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 10 to 50 mg of phenol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippinocott Co., Philadelphia, pp. 1037–1040, 1955.

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

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 892–893, 1977.

(4) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 940, 1976.

(5) OTC Volume 060053.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 900–901, 1973.

(7) Freeman, M. V., J. H. Draize, and E. Alvarez, "Cutaneous Absorption of Phenol," *Journal of Laboratory and Clinical Medicine,* 38:262–266, 1951.

(8) Deichmann, W. B., "Local and Systemic Effects Following Skin Contact with Phenol—A Review of the Literature," *Journal of*

Industrial Hygiene and Toxicology, 31:146–154, 1949.

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

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

(11) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 990–991, 1975.

h. *Phenolate sodium (sodium phenolate).* The Panel concludes that phenolate sodium is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Phenolate sodium, also known as sodium phenolate, sodium phenate, sodium carbolate, sodium phenoxide, and phenol sodium, is the sodium salt of phenol (carbolic acid) (Ref. 1). Ordinarily, phenol exists in the enol form; that is, it is a benzene ring with a hydroxyl group. Phenol has high resonant energy and can revert to the keto form (Ref. 2). This keto-enol type of isomerization is encountered from time to time in various organic compounds. The keto form is less stable than the enol form. The sodium salt is formed with the keto form. One hydrogen atom on position 2 is replaced with the metalic ion. Phenols are consideed stronger acids than other alcohols or water, but are weaker acids than carboxylic acids. The dissociation constant of phenol is 1.3×10^{10} as compared to 4.3×10^{7} for carbonic acid. Phenol reacts with sodium hydroxide to form a water-soluble salt, but it will not interact with sodium carbonate to form a salt.

Phenolate sodium is a white to reddish deliquescent substance composed of rods or granules. It is readily decomposed by carbon dioxide to phenol and sodium carbonate if it stands in the air. It must be stored in tightly closed containers. Phenolate sodium is strongly alkaline and caustic. It is very soluble in water, and alcohol-aqueous solutions are strongly alkaline and caustic. Phenolate sodium releases 81 percent phenol on decomposition or acidification. Phenol is less acidic than carbonic acid. The therapeutic and toxic effects of phenolate sodium are due to the phenol released (Refs. 1, 2, and 3).

(1) *Safety.* The Panel concludes that phenolate sodium is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The safety considerations for phenolate sodium are the same as those for phenol, because it releases phenol, and its toxic effects are due to the phenol (Ref. 1). In addition, phenolate sodium may augment the caustic effects of phenol due to the presence of sodium hydroxide, from which it is formed, if concentrated solutions are ingested orally or applied topically. Phenolate sodium precipitates proteins and can, therefore, exert an antimicrobial effect, as does phenol. The Panel has considered the antimicrobial effects of phenol and phenolate sodium elsewhere in this document. (See part IV. paragraph B.3.s. below—Phenolate sodium.)

Phenolate sodium, in doses of 0.1 to 0.3 g, was formerly used to treat diarrhea.

(2) *Effectiveness.* The Panel concludes that phenolate sodium is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Aqueous solutions of phenolate sodium are alkaline and caustic, but dilute solutions can be used to obtain the same anesthetic/analgesic effect on the mucous membrane as phenol (Ref. 1). Since solutions containing phenolate sodium are alkaline, the effects of certain ingredients that are physiologically active in the form of a base are assured when they are used in combination with phenolate sodium. This is the case when phenolate sodium is combined with nitrogenous topical anesthetics/analgesics. The released phenol and alkali may enhance the effects of the latter compounds and maintain an alkaline medium. Phenolate sodium is not the sole ingredient in any of the products submitted to the Panel for consideration, but has been submitted in combination with other topical anesthetic/analgesic ingredients.

The duration of action of aqueous solutions of phenolate sodium used as rinses, mouthwashes, and gargles is usually short and seldom lasts more than 5 or 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a concentration of sodium phenolate in aqueous solution, equivalent to a 0.5- to 1.5-percent concentration of phenol, in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge, containing a concentration of phenolate sodium which is equivalent to 10 to 50 mg of phenol, every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and suprvision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

Reference

(1) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 958, 1960.

(2) Noller, C. R., "Chemistry of Organic Compounds," W. B. Saunders Co., Philadelphia, pp. 489–490, 1951.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1079, 1976.

i. *Salicyl alcohol.* The Panel concludes that salicyl alcohol is safe and effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The chemical structure of salicyl alcohol is ortho-hydroxy benzyl alcohol. Actually, it is benzyl alcohol with a hydroxyl group on the number 2 position of the benzene ring. Salicyl alcohol occurs in plates or crystalline powder which melts at 86 to 87° C. It sublimes at 100° C. It is soluble in water, 1 part in 15, and very soluble in alcohol, chloroform, ether, and benzene (Ref. 1).

Salicyl alcohol is the hydroxy type of topical anesthetic/analgesic. It is only suitable for surface anesthesia. As is the case with other alcohols, it is not suitable for injection because it is feeble and causes neurolysis and sloughing of parenteral tissues. It is a neutral substance and does not depend upon ionization or basicity for its pharmacologic effects.

(1) *Safety.* The Panel concludes that salicyl alcohol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

A study cited by Sollmann (Ref. 2) found that salicyl alcohol is the most effective, the least toxic, and least irritant of the phenyl carbanols. Its toxicity is much lower than that of the "caine" type drugs. Presumably, it is metabolized in the body. Toxicity data are not available. No fatalities in man have been recorded.

The Panel was unable to find any data on the acute animal toxicity and chronic human toxicity of salicyl alcohol except in certain formulations for OTC preparations because it has fallen into disuse. It appears to have no adverse effects on the mucous membranes in concentrations of 6 percent or less. It is not caustic as are the phenolic type of alcohols.

(2) *Effectiveness.* The Panel concludes that salicyl alcohol is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Salicyl alcohol is an effective topical anesthetic/analgesic on the mucous membranes in concentrations of 1 to 6 percent in aqueous solution. Its onset of action is rapid, requiring 2 to 3 minutes. The duration of action, like that of the other hydroxy-type local anesthetics/analgesics is brief. The duration of action of aqueous solutions of salicyl alcohol used as rinses, mouthwashes, and gargles is usually short and seldom last more than 5 to 10 minutes. When incorporated in lozenges that slowly release the ingredient, anesthesia/analgesia lasts as long as effective concentrations are supplied to relieve pain of sore mouth or sore throat.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 1.0- to 6.0-percent concentration of salicyl alcohol in aqueous solution in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 50 to 100 mg of salicyl alcohol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

Reference

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1079, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 278, 1948.

Category I Labeling

a. *Indication.* "For the temporary relief of occasional minor irritation, pain, sore, mouth, and sore throat."

b. *Warnings*—(1) *For all drug products containing oral health care anesthetic/analgesic active ingredients.* (i) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(ii) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(2) *For oral health care anesthetic/analgesic products used in the form of gargles, mouthwashes, and mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which anesthetic/analgesic active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are mesbranded.*

The Panel recommends that the Category II conditions be eliminated from OTC oral health care anesthetic drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

Antipyrine.
Camphor.
Cresol.
Dibucaine.
Dibucaine hydrochloride.
Lidocaine.
Lidocaine hydrochloride.
Pyrilamine maleate.
Tetracaine.
Tetracaine hydrochloride.

a. *Antipyrine.* The Panel concludes that antipyrine is not safe and not effective for topical use as an anesthetic/analgesic on the mucous membranes of the mouth and throat.

Antipyrine is a pyrazolon derivative. Antipyrine is 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one. It exists as tubular crystals or as a white powder that is odorless and has a slightly bitter taste. It is also known as phenazone. It melts at 111° C (Ref. 1). One gram dissolves in less than 1 mL water, 1.3 mL alcohol, 1 mL chloroform, and 3.4 mL of ether. Aqueous solutions are neutral. Antipyrine was introducted as a medicine in 1887 (Ref. 2).

Antipyrine was synthesized by Knorr in 1883 in an attempt to prepare a substance that would be similar to quinine. It is administered orally as an anesthetic and antipyretic. It may be synthesized by several methods. One method involves the interaction of phenyl hydrizine and ethyl acetoacetate followed by methylation.

Antipyrine is incompatible with many substances, the most important of which are acetanilid, chloral, phenacetin, phenol, thymol, phenyl salicylate, sodium salicylate, various alkalis, alum, ammonia water, resorcinol, sodium bicarbonate, tannic acid, ferric chloride, and various other compounds (Ref. 3).

(1) *Safety.* The Panel concludes that antipyrine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The oral LD_{50} in rats is 1.8 g/kg. Large doses may cause nausea, vomiting, tremors, dizziness, weakness, diaphoresis, cyanosis, angioedema, and skin eruptions. It may produce methemoglobinemia in human beings, but this is rare. The skin eruptions may be macular, patchy, round or oval, varying in size, pink or dark purple, and persisting for a month or more after the drug has been withdrawn. Fixed pigmented areas occasionally result following its ingestion. Overdoses may produce stomatitis, drowsiness, convulsions, coma, and amaurosis (Ref. 3).

Antipyrine is absorbed from the mucous membranes of the mouth and throat. Some of its effects are systemic, although it allegedly has both local and systemic anesthetic effects. Swelling of the lips and the tongue and severe laryngeal edema interfering with respiration have occurred. A blue-grey coloration of the urine, which is green in reflected light, has been observed after large doses of antipyrine have been ingested (Refs. 2 and 3).

Antipyrine stimulates microsomal enzymes. It has been known to act additively with morphine. It combines with plasma proteins in a ratio of 1:8. Antipyrine is rapidly and completely absorbed from the gastrointestinal tract of man. Peak plasma levels are attained within 1 to 2 hours. It is slowly metabolized and disappears from the plasma at the rate of 6 percent per hour. The drug is rapidly metabolized in dogs and rabbits. The distribution depends on the water content of the tissue. It is metabolized by oxidation to form 4-hydroxy antipyrine (30 to 40 percent). This, in turn, is conjugated with glucuronic acid and excreted into the urine. Approximately 5 percent is excreted into the urine unchanged. Antipyrine does not produce euphoria, psychic or physical dependence, or withdrawal symptoms when administration is terminated. Cases of mild degrees of tolerance and habituation have been reported, but this has not been a problem. Antipyrine augments the doses of narcotics, analgesics, barbiturates, and hypnotics when ingested systemically.

Antipyrine is considered to be an unsafe drug because it produces severe cutaneous reactions. These are all believed to be due to sensitization. Of 394 cases of antipyrine poisoning reported prior to 1950, and reviewed by Greenberg (Ref. 4), 77 percent were of an allergic nature, 18 percent nonallergic, and in 5 percent the cause was undetermined. The most striking feature of the antipyrine hypersensitivity reaction is a fixed pigmented erythema. This was originally described by Brodie, et al. (Ref. 5). Ulceration of the buccal mucosa and erythematous pigmented lesions on the hands and the body have been noted. The Black race appears to be more susceptible to the stomatitis than other races. The majority of cases found in the literature concerning the toxicity of antipyrine indicate that the reported reactions are due to hypersensitivity.

The oral lethal dose of antipyrine in several species has been reported to be 1,000 mg/kg or more (Ref. 1). Thus, the main consideration of the Panel is the association between the use of antipyrine and the occurrence of fixed pigmented erythema of the skin and other types of skin reactions.

Antipyrine has fewer side effects than aspirin systemically. It does not interfere with the blood-clotting mechanisms as does aspirin. In addition, there is no evidence that antipyrine causes hepatotoxicity as does acetaminophen.

Antipyrine must not be confused with aminopyrine which, even though it is chemically allied, is known to cause irreversible agranulocytosis. Greenberg (Ref. 4) has indicated that only two cases of agranulocytosis due to antipyrine use were reported prior to 1950, and even in these it was not conclusive that antipyrine was the causative factor. No other cases have been reported since that time. Antipyrine, though closely related chemically to aminopyrine, is metabolized in a different manner, which is a possible explanation for differences in the propensity of aminopyrine to produce agranulocytosis.

The Panel has read with interest the comments of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products in which disagreement on antipyrine safety resulted in submission of both a majority and a minority report (42 FR 35436–35439). That Panel agreed that antipyrine may have merit and that, in spite of its long-term use in medicine, it has not been adequately evaluated for safety and effectiveness based on data from controlled studies. The minority felt that testing would be hazardous because of the known side effects due to sensitivity. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products referred to the position of FDA concerning the use of antipyrine as an analgesic in earwax softening preparations. That Panel, in its review of OTC topical otic drug products, published in the **Federal Register** of December 16, 1977 (42 FR 63564), recommended that such preparations be available by prescription only and not be available OTC.

(2) *Effectiveness.* The Panel concludes that antipyrine is not effective as an OTC anesthetics/analgesics active ingredient for topical use on the mucous membranes of the mouth and throat.

There are no data substantiating the fact that antipyrine acts as a stabilizer of the axonal membrane as do the topical local anesthetics. There are data indicating that antipyrine enhances the blockade caused by cocaine on isolated nerves in frogs, but in does not by itself produce a neuronal blockade.

Antipyrine is a anesthetic and a mild antipyretic systemically. Topically, antipyrine has been reported to be a feeble anesthetic and antiseptic (Ref. 3) and also to have some anesthetic effect on nerve endings (Refs. 2 and 6). It may cause constriction of the superficial blood vessels. Antipyrine has been used for the treatment of inflammatory conditions of the mucous membranes of the mouth and throat and for laryngitis in concentrations ranging from 5 to 15 percent. A solution of antipyrine composed of 5.4 percent antipyrine and 1.4 percent benzocaine in glycerin was formerly used for the treatment of acute otitis media (inflammation of the middle ear). Antipyrine has been used as a styptic for nasal hemorrhage. Antipyrine has a feeble antimicrobial effect, but this is of no consequence in considering such effects on the mucous membranes of the mouth and throat.

(3) *Evaluation.* The Panel concludes that antipyrine is not safe because it causes sensitization and adverse systemic reactions. In addition, antipyrine apparently manifests no significant topical anesthetic effects.

References

(1) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 90, 1960.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, pp. 525–527, 1948.

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, p. 150, 1973.

(4) Greenberg, L. A., "Antipyrine: A Critical Bibliographic Review," Hillhouse Press, New Haven, CT, pp. 44–45, 1950.

(5) Brodie, B. B., et al., "The Estimation of Antipyrine in Biological Materials," *Journal of Biological Chemistry,* 179:25–29, 1949.

(6) Sollmann, T., "The Comparative Efficiency of Local Anesthetics," *Journal of the American Medical Association,* 70:216–219, 1918.

b. *Camphor.* The Panel concludes that camphor is not safe and not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Camphor is a member of a cyclic group of hydroaromatic substances known as terpenes (Refs. 1 and 2). Camphor is 2-bornanone, a 2-ketone of heptane, which is naturally occurring in the camphor tree (*Cinnamum camphora*), an evergreen native to Eastern Asia. Natural camphor is obtained from all parts of the camphor tree. Camphor is also made synthetically from alpha pinene, a constitutent of turpentine. Approximately three-fourths of the camphor used is prepared synthetically. Natural camphor is optically active. Natural camphor is dextrorotatory, while the synthetic preparation is racemic and optically inactive. Both forms are pharmacologically active. Camphor melts at 174° to 177° C at atmospheric pressure. It sublimes readily. At 25° C, 1 g dissolves in 800 mL water, 1 mL ether, 1 mL alcohol, 0.5 mL chloroform, 0.4 mL acetone, and 1.5 mL turnpentine. Camphor, since it is a ketone, is converted by reduction to borneol, a secondary alcohol. Camphor has a peculiar tenacity and cannot be powdered in a mortar until it is moistened with an organic solvent. It liquifies when tribturated with menthol, thymol, phenol, and resorcinol. It is not compatible with oxidants such as potassium permanganate. Camphor forms complexes with cresol (camphor metacresol) from which both ingredients and other phenols can be released. Camphor is freely miscible with volatile and fixed oils. When applied to the skin and mucous membranes, camphor produces a feeling of warmth and provides a mild local anesthetic action that may be followed by numbness (Refs. 1 and 3).

Several camphor products are described in the official compendia. Camphor liniment, as listed in "National Formulary X", contains 20 percent camphor in cottonseed oil. This preparation is commonly called "camphorated oil." Other topical products containing camphor are camphor and soap liniment (4.5 percent

camphor) in "United States Pharmacopeia XIII", camphor spirit (10 percent camphor) in "National Formulary X", and camphor ointment (20 percent camphor) in "National Formulary IX" (Ref. N–6).

(1) *Safety.* The Panel concludes that camphor is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Camphor is absorbed from the mucous membranes and at the mucocutaneous junctions. Camphor is absorbed if injected subcutaneously. It is also absorbed from intact and damaged skin since it is nonionized and lipophilic. Excessive oral doses may be fatal (Ref. 3). Camphor is metabolized when ingested orally or assimilated by other routes. The camphor is first oxidized by the liver to campherol, and the campherol is then conjugated with glucuronic acid by the liver. The conjugate is excreted in the urine.

Camphor's minimal lethal/dose for rabbits is 2 g/kg orally. The median lethal dose (LD_{50}) subcutaneously for rats is 2.2 g/kg. The oral median lethal dose for guinea pigs is 180 mg/kg. In mice, the LD_{50} is 30 mg/100 g when administered intraperitoneally. The estimated minimal lethal dose for humans when ingested orally is 2 g. One adult survived ingestion of 1.5 g of camphor. Ingesting 0.7 to 1.0 g of camphorated oil proved fatal to a child (Ref. 5). Accidental poisoning has occured from ingesting the oil when it has erroneously been administered for castor oil. Cases of poisoning continue to be reported. The Panel considered various reports and editorials submitted to it concerning the toxicity and frequency of poisonings from camphor-containing preparations, particularly in children. The Panel has taken cognizance of these cases and those that continue to occur. However, the Panel is unaware of any case of poisoning that has occurred from topical administration on the skin in spite of the fact that camphor is known to penetrate the skin due to its lipophilic nature. The Panel is also aware of the fact that camphor is readily absorbed from the mucous membranes of the mouth, throat, and gastrointestinal tract.

Camphor is used as a component of paregoric (camphorated tincture of opium), which is widely used as an antidiarrheal in adults and children, and as a sedative and anesthetic in infants and children. However, no documented justification for its use systemically or topically on the mucous membranes has been found. The Panel, therefore, considers camphor not safe as a topical anesthetic/analgesic on the mucous membranes. Camphor in oil was once used parenterally as an analeptic, but it has long since been abandoned for this purpose. Systemically, camphor stimulates the central nervous system. Toxic doses produce convulsions which may be fatal. Camphor is not a common skin sensitizer but can, in concentrations above 3 percent, be an irritant. It is used as a counterirritant on the skin in topical antirheumatic preparations (Ref. 3). Its sensitizing potential on the mucous membranes is not known.

(2) *Effectiveness.* The Panel concludes that camphor is not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The Advisory Review Panel on OTC External Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products has evaluated the topical use of camphor as an analgesic, an anesthetic, and as a counterirritant (44 FR 69802). That Panel's recommendations and conclusions were published in the **Federal Register** of December 4, 1979 (44 FR 69768). In concentrations of 3 percent or less by weight, camphor is an effective antipruritic and relieves the discomfort due to skin lesions characterized by itching and burning on the skin at the site of application. It is believed to act upon sensory receptors in the skin and mucous membranes in the same manner as the hydroxy or alcohol types of topical anesthetics even though it is a ketone. In concentrations exceeding 3 percent, particularly if combined with other ingredients that produce counterirritation, camphor stimulates the nerve endings in the skin and induces relief of pain and discomfort in muscles, joints, and other subcutaneous structures at a site distant to its application on the skin. The Panel does not find any data establishing camphor as an effective topical anesthetic/analgesic ingredient for topical use on the mucous membranes of the mouth and throat. When camphor is injected internally it produces a sensation of warmth. Numerous clinical reports regarding the ability of camphor to relieve cutaneous itch are available (Refs. 1, 3, and 6).

Camphor most likely exerts its anesthetic effects in a manner similar to that manifested by the hydroxy or alcohol type of compounds. When applied to the skin or mucous membranes, it produces a sense of warmth followed by a sensation of numbness. Topically, camphor is weakly antiseptic, but this attribute is of no practical significance as far as effective antimicrobial activity in the oral cavity is concerned. The odor of camphor may play a role in the relief of pain (Refs. 1, 3, and 6). The psychological component of the effect of drugs in causing pain relief by their placebo effect cannot be ignored when used topically on the skin, but it is doubtful that this mechanism operates when the drug is used on the mucous membranes.

(3) *Evaluation.* There are no well-documented studies that show that camphor is an effective active ingredient for topical use on the muscous membranes of the mouth and throat in a dosage range that does not irritate tissues. The fact that camphor is effective when used topically on the skin does not support the contention that it is equally as useful on the mucous membranes. Camphor is readily absorbed and has resulted in fatalities when taken internally and is therefore not a safe ingredient for use on the mucous membranes.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 219–220, 1976.

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

(3) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 993, 1970.

(4) Osol, A., et al., "The Dispensatory of the United States of America," 1950 Ed., J. B. Lippincott Co., Philadelphia, pp. 208–209, 1950.

(5) Smith, A. G., and G. Margolis, "Camphor Poisoning: Anatomical and Pharmacologic Study; Report of a Fatal Case; Experimental Investigation of Protective Action of Barbiturate," *American Journal of Pathology,* 30:857–869, 1954.

(6) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 249–252, 1957.

c. *Cresol.* The Panel concludes that cresol is not safe and not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The description of cresol and its safety appears in detail in the section on antimicrobial agents described below. (See part IV. paragraph B.2.d. below—Cresol).

(1) *Safety.* The Panel concludes that cresol is not safe as an OTC anesthetic/

analgesic active ingredient for topical use on the mouth and throat.

(2) *Effectiveness.* The Panel concludes that cresol is not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mouth and throat.

Since cresol is an aromatic alcohol and structurally and chemically similar to phenol, it behaves like phenol pharmacologically (Refs. 1, 2, and 3). Cresol is rapidly absorbed from the skin and mucous membranes and is somewhat less toxic than phenol, but exerts similar caustic and protein-denaturing qualities. When applied locally to the skin, cresol causes an erythema and burning sensation followed by numbness (Ref. 4). It acts in the same manner as phenol and destroys tissue, cauterizing the area of application.

Dilute solutions of cresol possess a topical anesthetic activity similar to that of the hydroxy type of local anesthetics. It is, however, not recommended or used for this purpose.

(3) *Evaluation.* Cresol is a phenolic derivative with antimicrobial and topical anesthetic activity. The Panel concludes that cresol is not safe for use as an anesthetic/analgesic on the mucous membranes of the mouth or throat.

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadephia, pp. 809–810, 1957.

(2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 2d Ed., The Macmillan Co., New York, p. 1081, 1960.

(3) OTC Volume 130006.

(4) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott Co., Philadelphia, pp. 341–342, 1967.

d. *Dibucaine.* The Panel concludes that dibucaine is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

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

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

The hydrochloride salt is a white, tasteless powder which melts at 90° to 98° C. The melting point is not sharp. It is very soluble in water (one part dissolves in 0.5 part water) and in organic solvents, such as benzene, acetone, and chloroform. It is insoluble in ethers and oils. Aqueous solutions have a pH range of 6.2 to 6.5. Alkaline substances, such as the hydroxides, carbonates, and bicarbonates, readily precipitate the base from aqueous solutions. Solutions must be prepared in distilled water and stored in alkaline-free glass; otherwise, the drug precipitates out due to the reaction with the alkali in the glass. Solutions of salts of dibucaine are stable when boiled. Dibucaine is compatible with epinephrine. The general "United States Pharmacopeia" name and the one that is accepted is dibucaine. The hydrochloride salt is more stable thant the base (Refs. 1, 2, 4, and 5). Solubility of the salt in oils or nonwater-soluble bases is poor. It is soluble in glycols.

(1) *Safety.* The Panel concludes that dibucaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine is a synthetic topical anesthetic of the amide type derived from quinoline (Refs. 2 and 6). It is a base that forms salts with various acids. The most frequently used salt is the hydrochloride. Dibucaine is a "caine" type drug and closely follows the characteristic chemical configuration of this type drug in having an amino group, dimethylene chain, and aromatic nucleus. Dibucaine is approximately 15 times more potent and toxic than procaine, which has been used as the reference standard in clinical studies. Since it is more potent and more toxic on a parallel basis, only one-fifteenth would be required to achieve the same effect as procaine. The absolute toxicity is 15, but the relative toxicity compared to procaine is 1. Toxicity, of course, depends upon the site and mode of application, and the vascularity of the tissues as well as the mode and rate of biotransformation. The lethal dose in human beings, therefore, is unknown. It is one of the most potent and longest lasting of the topical anesthetics. In mice, the acute intravenous LD_{50} is 2.8 mg/kg compared to 21 mg/kg for procaine and 11 mg/kg for cocaine. In rabbits, dibucaine is six times as toxic as cocaine given intravenously (Ref. 7). Dibucaine produces central nervous system stimulation and myocardial depression characteristic of the "caine" type of drugs when recommended doses are exceeded and high plasma levels result. Fatalities have been reported from the use of the maximal tolerable dose following infiltration, perineural injection, or topical application to the mucous membranes. Fatalities have not been reported following the use of dibucaine-containing products after application to the mucous membranes as a prescription item. Ten cases of acute intoxication, five of which were fatal, have been reported after the oral ingestion of dibucaine. In nine of those cases, the drug was prescribed for rectal use; in one case intoxication followed the use of ointments and creams marketed OTC for topical use. Five fatalities due to accidental ingestion of OTC ointments by children have been reported. These cases were documented in an adverse reaction reporting system extending from 1951 to 1972 (Ref. 8).

During the long period of marketing experience, reactions on the skin and mucous membranes due to irritancy and allergy have been low. Patch testing in controlled studies in humans, and a review of the literature by Lane and Luikart (Ref. 9) reveal that the incidence of sensitization reactions is low and no greater than that observed with procaine, tetracaine, benzocaine, and cyclomethycaine. Dibucaine can act as a hapten and be antigenic. Anaphylactic and other allergic types of reactions are possible, but have not been reported after topical use on the skin or mucous membranes after rectal and oral use.

Dibucaine has been alluded to as a "highly toxic" anesthetic by physicians. Relatively speaking, however, it is no more toxic than procaine, tetracaine, lidocaine, and similarly acting drugs if used in proper dosage and with the same precautions. Its chief danger lies in its potency, since one-tenth to one-fifteenth as much would be required to produce a toxic reaction compared to lidocaine or procaine. Too liberal use of a preparation from topical application to mucous membranes or over wide areas of damaged or abraded skin from which the drug is readily absorbed could result in severe and often fatal systemic reactions. Absorption from the oral cavity can be rapid and result in high plasma levels. Systemic absorption may

result in convulsions, myocardial depression, and death (Ref. 5). Dibucaine must not be ingested orally because it is absorbed from the intestines. Sensitization can occur but is uncommon.

(2) *Effectiveness.* The Panel concludes that dibucaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine is one of the most potent and longest lasting topical anesthetics. It is approximately 15 times more potent than procaine and 3 to 6 times more potent than cocaine. As is the case with other topical anesthetics, it acts by stabilizing the neuronal membrane of the pain receptors in the mucous membranes. It has been used extensively for spinal anesthesia, topical anesthesia on the mucous membranes and skin, and to a lesser extent for infiltration and nerve blocking. Its period of latency when used intrathecally may be as long as 10 minutes. Its duration of action introthecally is approximately 3 hours. This latency and long duration of action are also reflected when used by other routes (Ref. 2). The base readily penetrates the intact skin and mucous membranes. It acts superficially on the mucous membranes and not on the deeper structures below. The concentrations absorbed systemically from the mucous membranes are significant and may result in high plasma levels, which may cause fatal systemic reactions. In view of this, the Panel regards the drug as too hazardous for OTC use in the oral cavity and emphasizes that it should be administered by a physician familiar with its hazards and use.

(3) *Evaluation.* The Panel concludes that dibucaine in not a suitable OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat because of its rapid absorption which may result in fatal systemic toxicity.

References

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

(2) Adriani, J., "Local Anesthetics," *in* "The chemistry and Physics of Anesthesa," 2d Ed., Charles C. Thomas, Springfield, IL, pp. 398–473, 1962.

(3) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al. Mack Publishing Co., Easton, PA, p. 990, 1975.

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

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

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

(7) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 434–436, 1955.

(8) OTC Volume 060013.

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

e. *Dibucaine hydrochloride.* The Panel concludes that dibucaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The general characteristics of dibucaine hydrochloride have been discussed elsewhere in this document. (See part III. paragraph B.2.d. above—Dibucaine.)

(1) *Safety.* The Panel concludes that dibucaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The remarks above concerning the safety of dibucaine base are also applicable to the hydrochloride. (See part III. paragraph B.2.d. (1) above—Safety.) As is the case with salts of other topical anesthetics, dibucaine hydrochloride penetrates epithelial barriers and exerts an anesthetic effect on pain receptors and other receptors with which it comes into contact and on receptors in structures immediately beneath the epithelial layers. It passes into the tissue fluids and gains access to the systemic circulation. Since dibucaine is approximately 15 times more potent and toxic than procaine, the quantity used in an OTC preparation could result in high plasma levels and serious systemic responses. Reactions from the use of therapeutic doses on the mucous membranes are uncommon but do occur (Ref. 1).

Systemic absorption can result in convulsions, myocardial depression, or death (Ref. 1). Dibucaine hydrochloride is readily absorbed from the mucous membranes. It is also absorbed from open lesions or broken or abraded skin, but not from the intact epithelial barriers (Refs. 2 and 3). The possibility that sufficient quantities may be absorbed from mucous membranes and cause fatal reactions is great. The Panel also calls attention to the greater solubility of the hydrochloride in the water of tissue fluids than the solubility of the base. However, the hazard from rapid aborption from either the salt or the base is almost equally as great.

Sensitization can occur and has been reported but is uncommon.

(2) *Effectiveness.* The Panel concludes that dibucaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Dibucaine hydrochloride is converted to the base when absorbed by mucous membranes from the buffering mechanisms in the tissues. Its mechanism of action is similar to dibucaine base.

There are well-controlled studies documenting the effectiveness of dibucaine hydrochloride as an anesthetic/analgesic for topical use of the mucous membranes of the mouth and throat. Dibucaine hydrochloride enjoys wide use and clinical acceptance. However, based upon published reports in the literature and due to the danger of fatal reactions, the Panel concludes that dibucaine hydrochloride should be used topically as an anesthetic/analgesic active ingredient on the mucous membranes as a prescription drug only and not for OTC use.

(3) *Evaluation.* The Panel concludes that dibucaine hydrochloride is not a suitable OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat because of its rapid absorption which can result in fatal systemic toxicity.

References

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

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

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

f. *Lidocaine.* The Panel concludes that lidocaine is effective but not safe as an OTC anesthetic/analgesic for topical use on the mucous membranes of the mouth and throat.

Lidocaine is an amide type of topical anesthetic and thus differs from tetracaine, benzocaine, and procaine which are esters of paraminobenzoic acid. Lidocaine is 2-(diethylamino)-2', 6'-acetoxylidide (Ref. 1). It can also be considered an acetamide with one of the hydrogen atoms on the amino group of the amide portion of the compound replaced by a dimethyl aniline group

and one of the hydrogen atoms on the terminal carbon atom replaced by a nitrogen atom with two ethyl groups. It is a tertiary amine and is, therefore, a base that forms salts with acids (Ref. 2). The salt used clinically is the hydrochloride.

Lidocaine was synthesized by Lofgren in 1946 in Sweden (Ref. 3). Lidocaine base is a white to slightly yellow crystalline powder having a characteristic aromatic odor. It is practically insoluble in water, very soluble in alcohol and chloroform, freely soluble in ether, and dissolves in oils. Lidocaine is more lipophilic than procaine. Lidocaine base melts between 66° and 69° C (Ref. 4). Lidocaine base for use as a topical anesthetic/analgesic on the mucous membranes is incorporated in water-miscible solvents such as polyethylene glycol, propylene glycol, and methyl cellulose (Ref. 5). It may also be used in aqueous solutions.

Lidocaine salts are highly stable in vitro. The hydrochloride endures 8 hours when boiled with 30-percent hydrochloric acid, or after lengthy heating with alcohol and potassium hydroxide (Ref. 2). However, it is readily metabolized in the body. Up to 11 percent of the usual doses used for regional block in humans are recoverable in the urine within 4 hours (Ref. 6). The hydrochloride salt is not easily isolated from the solution.

(1) *Safety.* The Panel concludes that lidocaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Although lidocaine base is poorly soluble in water, it is readily absorbed when applied over mucous membranes. If sufficient quantities are absorbed, plasma levels may be attained that result in systemic pharmacological reactions characteristic of the "caine" type drugs which may be fatal (Ref. 7). Reactions due to systemic absorption are of the central nervous system type and the cardiovascular type. Stimulation of the cortex occurs first, followed by depression of not only the cerebral cortex, but lower centers as well (Ref. 8). Slow onset of a reaction causes stimulation followed by depression leading to drowsiness, nervousness, dizziness, blurred vision, nausea, tremors, convulsions, and respiratory arrest. When the onset is rapid, central nervous system depression occurs, leading primarily to unconsciousness which may be followed by respiratory arrest (Ref. 7). Myocardial depression and cardiac arrest may occur simultaneously. In addition, a fall in blood pressure and intercostal paralysis is regarded as a potential hazard resulting from high plasma levels (Ref. 9).

Lidocaine is used intravenously in small quantities by internists. Lidocaine has useful antiarrhythmic activity attributed to an increase of the electrical stimulation threshold of the ventricle during diastole. The antiarrhythmic action is similar to that of procainamide and quinidine but, because of its short duration of action, lidocaine hydrochloride must be given by continuous intravenous infusion if the action is to be sustained. The antiarrhythmic action usually develops within a few minutes and has a duration of 10 to 20 minutes, following a single intravenous injection of 50 to 100 mg. When it is used intravenously at the rate of 10 to 45 microgram/kilogram (μg/kg) of body weight per minute, the antiarrhythmic action begins to develop in 10 to 20 minutes. Blood levels of 1.0 to 2.5 μg/ml appear to be required for suppression of ventricular arrhythmias. These blood levels may be attained with an intravenous priming dose or by continuous infusion of the drug. Blood levels exceeding 5 μg/ml may, however, prove toxic and cause convulsions and cardiac depression. Constant electrocardiograph monitoring is used to avoid overdosage and toxicity.

Manufacturers of lidocaine indicate that its specific indication is for the drug management of ventricular arrhythmias occurring during cardiac manipulation, such as cardiac surgery. It is used for life-threatening arrhythmias, particularly those which are ventricular in origin, such as occur during acute myocardial infarction (Refs. 10 and 11).

Approximately 90 percent of a dose of lidocaine is metabolized by the enzmes in the microsomes of the liver within 4 to 5 hours, and the metabolites are excreted along with 10 percent of the unchanged drug in the urine. Lidocaine is metabolized by several metabolic pathways in the liver. The enzymes involved are oxidases and amidases. Several metabolites have recently been found which produce convulsant activity. These may account for delayed reactions due to cumulative effects. Lidocaine is not hydrolyzed by the plasma cholinesterases as are tetracaine, procaine, and other esters of aminobenzoic acid (Refs. 6 and 8).

Lidocaine base or its salts are not irritating to intact or abraded skin (Ref. 12). Lidocaine can produce sensitization after repeated contact, as do the "caine" type drugs, despite statements made to the contrary. However, the incidence of sensitization is low (Ref. 7). The statement has appeared in the medical literature that the amide type of the "caine" topical anesthetics is devoid of sensitizing potential (Ref. 8). Such a statement cannot be supported either on a theoretical or factual basis. Most soluble drugs are capable of acting as haptens and forming antigens. They can produce antigens that stimulate production of immune bodies of the IgE type which cause allergic reactions in susceptible individuals. Anaphylaxis has been reported after application of lidocaine to the mucous membranes and infiltration. One case has come to the Panel's attention in which an anaphylactic reaction occurred following application to the skin (Ref. 13). The report, however, does not state whether the quantity, which was said to be minute, was injected to raise a skin wheal or applied by a patch or scratch test. In another case (Ref. 13), a female patient who alleged that she was allergic to lidocaine was tested for this allergy by instilling one drop into the conjunctival sac. The patient developed immediate syncope, circulatory collapse occurred, and then severe shock. After 2 hours of treatment with vasopressors, antihistamines, and steroids, she recovered.

(2) *Effectiveness.* The Panel concludes that lidocaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

There are well-controlled studies documenting the effectiveness of lidocaine as an anesthetic/analgesic for topical use on the mucous membranes of the mouth and throat. Lidocaine enjoys wide use and clinical acceptance, and its effectiveness has been documented in published reports in the literature, the Panel concludes that lidocaine should be available by prescription, and not be used as an OTC anesthetic/analgesic.

Lidocaine is approximately twice as potent and toxic as procaine on a weight bases (Ref. 7). The onset of anesthesia is rapid, after injection, requiring less than 1 minute. The onset of action when used on mucous membranes is 1 to 2 minutes. The base is poorly soluble in water but soluble in lipid substances such as glycols and similar types of solvents. The base penetrates the intact skin and exerts an anesthetic and antipruritic action in the skin (Ref. 12). The salts do not.

Lidocaine base is an effective topical anesthetic/analgesic on the mucous membranes. When properly formulated, with ingredients that insure its stability and continuous contact with an epithelial surface, it provides prolonged anesthesia. The pain-relieving action of lidocaine, as is the case with other topical anesthetics of the "caine" type, is entirely within the mucous

membranes. The quantity circulating in the blood is insufficient to provide anesthesia to parts of the body distal to the site of application in structures beneath the mucous membranes. Lidocaine blocks transmission at nerve endings by stabilizing the neuronal membrane in the same manner as do other topical anesthetics of the "caine" type (Ref. 2). Anesthesia of the mucous membranes persists for 20 to 30 minutes after application to a mucous surface.

(3) *Evaluation.* Lidocaine is an effective anesthetic/analgesic for topical use on the mucous membranes, but is rapidly absorbed and capable of producing toxic systemic reactions that can be fatal. The Panel concludes that it should remain a prescription item and concludes it is not safe as an OTC product for self-medication by a consumer.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 717, 1976.

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

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 666–669, 1973.

(4) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 992, 1975.

(5) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott, Philadelphia, pp. 653–654, 1960.

(5) OTC Volume 060020.

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

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

(8) Covino, B. G., "Local Anesthesia," *New England Medical Journal,* 286:975–983, 1972.

(9) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

(10) Moe, G.K., and J. A. Abildskov, "Antiarrhythmic Drugs," *in* "The Pahrmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co,. New York, pp. 696–697, 1975.

(11) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 13–18, 1977.

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

(13) Arens, J.F., Personal communication to J. Adriani, undated, contained in OTC Volume 130194.

g. *Lidocaine hydrochloride.* The Panel concludes that lidocaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Lidocaine hydrochloride is the salt of lidocaine base, a tertiary amine. The chemistry of lidocaine base has been described elsewhere in this document. (See part III. paragraph B.2.f. above—Lidocaine.) Lidocaine hydrochloride is a white crystalline powder with a slightly bitter taste. It melts between 74° and 79° C. It is very soluble in water, alcohol, and chloroform, but is insoluble in ether (Refs. 1 and 2). Lidocaine hydrochloride is very stable in vitro and withstands boiling in 30 percent hydrochloric acid for 8 hours or more. Aqueous solutions are acidic in reaction, the pH ranging from 5 to 6.4 (Ref. 3). The salt is highly ionized and not lipophilic. When injected into the tissues or applied on mucous membranes it is converted to the free base due to the buffering mechanisms present in the tissues. The free base is the physiologically active form of the drug. The nitrogen atom on the cation of lidocaine hydrochloride is converted from a tertiary atom to a quaternary atom (Ref. 4).

(1) *Safety.* The Panel concludes that lidocaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Lidocaine hydrochloride is very soluble in water. It is twice as potent and twice as toxic as procaine. It is readily absorbed from the mucous membranes of the mouth, pharynx, trachea, and bronchi. Absorption is followed by significantly perceptible blood levels that result in systemic toxicity if lidocaine hydrochloride is applied liberally.

Human toxicity varies with individual tolerance, age, sex, health status, and vascularity of the tissues. Convulsions and cardiac depression may occur if applied in excessive quantities (Refs. 5 and 6). The potential for sensitization exists, as with any other drugs, but it is not greater than with other topical anesthetics (Refs. 2 and 6). Topical irritancy is low, and rashes and other cutaneous lesions have not been reported. As is the case with other nitrogenous local anesthetics, lidocaine is dispensed as the hydrochloride salt because of its greater stability and ease of handling.

(2) *Effectiveness.* The Panel concludes that lidocaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The hydrochloride salt is acidic, is highly ionized, and is not strongly lipophilic; therefore, it does not readily penetrate epithelial barriers. It is active when it is converted to the base by the buffering mechanisms of the tissues. This occurs when it is injected perineurally or when it is applied to the mucous membranes.

Lidocaine acts by stabilizing the axonal membrane and preventing conduction in the nerve fibers connecting with receptors for pain and other stimuli in the skin. Adriani and Zepernick (Ref. 7) found that it rated fifth among 40 topical anesthetics tested on the tip of the tongue in deadening pain due to electrical stimulation. The free base is the physiologically active form. Additional data on effectiveness of lidocaine is described elsewhere in this document. (See part III. paragraph B.2.f. (2) above—Effectiveness.)

(3) *Evaluation.* Although lidocaine hydrochloride is an effective anesthetic, it is not safe for oral health care preparations intended for pain relief because it may be absorbed rapidly and cause tremors and often fatal toxic reactions, unless used with extreme caution.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 717, 1976.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, pp. 666–669, 1973.

(3) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 608, 1960.

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

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

(6) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 277, 1977.

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

h. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe but not effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Pyrilamine maleate is 20(2-dimethyl-aminoethyl) (para-methoxybenzyl)amino pyridine bimaleate. It is an antihistaminic drug that is a derivative of ethylene diamine. Pyrilamine maleate was first synthesized in France in 1946 and introduced as an antihistamine drug. It

was one of the first antihistaminic drugs to be introduced and has actions and uses of the class of therapeutic agents known as the antihistamines.

Pyrilamine maleate is a white crystalline powder with a faint odor. One gram dissolves in 0.5 mL water, 3 mL alcohol, and 2 mL chloroform. It is only slightly soluble in ether. It melts between 99° and 103° C. Pyrilamine maleate in a 10-percent solution has a pH of approximately 5.1 (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that pyrilamine maleate is safe as an anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Pyrilamine maleate is readily absorbed from the gastrointestinal tract. It is also absorbed to a variable extent, depending upon concentration and area exposed, from the mucous membranes of the mouth and throat. The absorbed drug in this manner produces systemic effects. In recommended doses, there is a remarkable lack of systemic toxicity (Refs. 3 and 4). Animal data on toxicity were not available to the Panel. The toxicity, according to Gosselin et al. (Ref. 5), is between 4 and 5. The most common side effect of pyrilamine maleate is sedation manifested by drowsiness. The sedative effect of the antihistamines is not unpleasant. In certain patients, particularly those of the ethylene-diamine type, antihistamines may have a stimulating effect. Other side effects of overdosage of pyrilamine maleate include euphoria, nervousness, insomnia, tremors, blurring of vision, diplopia, fatigue, loss of appetite, nausea, vomiting, epigastric distress, etc. If doses are increased, sedation may be replaced by irritability leading to convulsions, hyperpyrexia, and even death resulting from respiratory arrest (Ref. 6). Children are more likely to develop excitation, erythema, and marked hyperthermia with toxic doses. Milder forms of toxic reactions consist of visual disturbances, dizziness, confusion, irritability, and difficulty in coordination. Pyrilamine maleate may produce skin rashes and urticaria (hives) after oral administration or topical application (Refs. 7 and 8). Since pyrilamine maleate can act as a hapten, it can produce allergic reactions even though it is used for the treatment of patients with allergic conditions (Refs. 9 and 10). The simultaneous use of pyrilamine and alcohol or other central nervous system depressants has an additive effect which causes an enhancement of the depression (Refs. 3, 4, and 11).

(2) *Effectiveness.* The Panel concludes that pyrilamine maleate is not an effective anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Antihistamines have structures that are closely allied to structures of local anesthetics and may have anesthetic properties. This action has not been ascribed to pyrilamine (Ref. 10). The antihistamines, besides being competitive antagonists of histamine, also have, in addition to the central nervous system effect, anticholinergic and antiserotonin action (Ref. 12). Pyrilamine maleate may have a cocaine-like effect on catecholamine uptake. Pyrilamine maleate is readily absorbed from the gastrointestinal tract after oral administration. Its action is manifest within 15 to 20 minutes. The peak effect is attained in 1 hour, and it has a duration of 3 to 6 hours. Practically all the drug is metabolized and excreted in the urine unchanged (Ref. 13). It is the consensus of the Panel that any beneficial effects drived from pyrilamine maleate applied topically on the mucous membranes of the mouth and throat are due to its systemic effect after absorption, if sufficient quantities are applied, and not to any local effect on pain receptors (Refs. 3 and 13).

(3) *Evaluation.* The Panel concludes that pyrilamine maleate has no significant anesthetic/analgesic effect on the mucous membranes of the mouth and throat.

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 986, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1036, 1976.

(3) Loew, E. R., "The Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," *Animals New York Academy of Science,* 50:1142–1160, 1950.

(4) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews,* 27:542–573, 1947.

(5) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 232, 1976.

(6) Churchill, J. A., and G. D. Gammon, "The Effect of Antihistaminic Drugs on Convulsive Seizures," *Journal of the American Medical Association,* 141:18–21, 1949.

(7) Wyngaarden, J. B., and M. H. Seevers, "The Toxic Effects of Antihistaminic Drugs," *Journal of the American Medical Association,* 145:277–282, 1951.

(8) Sherman, W. B., "The Uses and Abuses of Antihistamine Drugs," *Bulletin of the New York Academy of Medicine,* 27–309–324, 1951.

(9) Marsh, D. F., and A. J. Davis, Jr., "Comparative Activity of Various Antihistaminic Substances Towards the Vasodepressor Response to Histamine," *Journal of Pharmacology and Experimental Therapeutics,* 89:234–246, 1947.

(10) Wells, J. A., "General Discussion I," *Annals New York Academy of Science,* 50:1202–1206, 1950.

(11) Curry, J. J., "The Action of Histamine on the Respiratory Tract in Normal and Asthmatic Subjects," *Journal of Clinical Investigation,* 25:785–791, 1946.

(12) Code, C. F., "The Mechanism of Anaphylactic and Allergic Reactions: An Evaluation of the Role of Histamine in Their Production," *Annals of Allergy,* 2:457–471, 1944.

(13) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 146–149 and 986, 1973.

i. *Tetracaine.* The Panel concludes that tetracaine is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine is one of the numerous soluble aminobenozic acid esters possessing topical anesthetic activity. Tetracaine is closely allied to procaine in chemical structure (Ref. 1). It has been available since 1932 for spinal, epidural nerve blocks, and topical anesthesia. In the structure of tetracaine, a butyl group is substituted for one of the hydrogen atoms of the amino group on the benzene ring of procaine. The two ethyl groups on the nitrogen atom of the amino ethanol portion of the procaine molecule are replaced by methyl groups. The molecule of tetracaine conforms to the general configuration characteristic of the "caine" type drugs that have an aromatic nucleus, an ester linkage, an intervening dimethylene chain, and a tertiary nitrogen atom. Shortening the ethyl groups to methyl groups and replacing the hydrogen atom on the amino group with a butyl radical increases the potency and toxicity of tetracaine approximately 10 times compared to that of procaine (Refs. 1 and 3). Tetracaine manifests topical anesthetic activity both internally on the mucous membranes and externally on the skin. The duration of action is approximately two to two-and-one-half times that of procaine. This is due to the fact that the protein-binding activity and the lipid solubility of tetracaine are increased over those of procaine by the alteration in structural configuration and by the increase in molecular weight (Ref. 3).

Tetracaine is a teriary amine and, therefore, is a base. It forms salts with various acids including hydrochloric acid. It is generally used in the form of its salts. One gram of the base dissolves in approximately 1,000 mL water. Tetracaine base is much more soluble in organic solvents than water. One gram of the base dissolves in 5 mL alcohol, 2 mL chloroform, and 2 mL ether.

Tetracaine base is less stable than its salts. It is readily soluble in oils and oleaginous bases. The base may be incorporated into water-soluble creams for topical use. It is not as readily released from petrolatum bases when applied topically as it is from water-soluble bases (Ref. 4).

Aqueous solutions of the base decompose rapidly upon standing. Tetracaine hydrochloride occurs as a fine white crystalline odorless powder which has a slightly bitter taste followed by a sense of numbness. Aqueous solutions of the hydrochloride are neutral or slightly acid to litmus. Solutions of the base are alkaline. One part of tetracaine hydrochloride is soluble in 7 parts of water. It is soluble in alcohol but insoluble in ether and benzene. Tetracaine hydrochloride melts between 147° and 150° C (Ref. 1).

Tetracaine salt solutions can be sterilized by boiling for short periods of time. Tetracaine hydrochloride powder or crystals, or aqueous solutions slowly undergo a chemical change and lose their anesthetic potency. The shelf life is limited to less than 1 year. The shelf lives of ointments and other preparations containing the base used topically are not known (Ref. 3).

(1) *Safety.* The Panel concludes that tetracaine is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Although tetracaine base is sparingly soluble in water, sufficient quantities can be absorbed from extensive areas of damaged skin or from the mucous membranes in quantities that produce adverse systemic effects (Ref. 3). High plasma levels of tetracaine will produce convulsions and cardiac depression as do other topical anesthetics of the "caine" type. Adriani and Campbell (Ref. 4) have indicated that the cardiovascular type of reaction may occur without central excitation and cause syncope (fainting) and cardiac arrest. This type of reaction often occurs abruptly without warning and is usually fatal (Ref. 5).

Tetracaine is 10 times more toxic than procaine when administered intravenously in animals. Its relative toxicity is equal to that of procaine since 1 mg is equal to 10 mg procaine in potency and toxicity. Due to its potency, dosages of tetracaine preparations are more difficult to control and over dosage occurs more readily than with less potent drugs. The intraperitoneal LD_{50} of tetracaine in mice is 70 mg/kg. Data on animal toxicity are not in agreement due to different methods of studying toxicity by different investigators. Rapid intravenous injection of tetracaine preparations into animals irrespective of species, causes convulsions and circulatory system depression (Ref. 6). The differences in results obtained by different investigators are merely quantitative. Qualitatively, the responses are the same.

Tetracaine appears to manifest a greater degree of myocardial depression than do other drugs of the "caine" type when the plasma concentrations reach toxic levels (Ref. 5).

Tetracaine is hydrolyzed by pseudocholinesterase in the blood as are procaine and other esters of paraminobenzoic acid. The rate of hydrolysis, however, is approximately one-fifth the rate of procaine (Ref. 3). This slower rate of detoxification contributes to the greater degree of toxicity it manifests compared to other drugs of the "caine" type.

Tetracaine manifests no well-defined chronic toxicity. Adverse reactions from repeated use have not been reported. The action perineurally is reversible, and no histological changes have been demonstrated in nerve tissues. The toxic dose in humans is not known. The maximum limit of dosage of tetracaine hydrochloride perineurally or by infiltation is considered to be between 75 to 100 mg in healthy adults. Topically, on the mucous membranes of the pharynx, the maximum dose is considered to range between 25 to 40 mg (Refs. 3 and 5). Tetracaine manifests no appreciable degree of irritancy when injected or applied topically. Since tetracaine can act as a hapten, it is capable of producing allergic-type reactions mediated by immunoglobulin E (Ref. 3). It may also, after repeated topical applications, cause the cytotoxic type of reaction (Refs. 3 and 5).

Tetracaine base is safe when applied to limited areas of damaged skin. It is also safe when applied to intact skin because absorption and penetration occur slowly. Tetracaine base is readily absorbed from all mucous membranes. High plasma levels may result, causing fatal reactions. The sensitizing potential of tetracaine is no greater than it is with other topical anesthetics. Since tetracaine is a derivative of paraminobenzoic acid, mention is frequently made of possible cross-sensitization with other aminobenzoates, but documentation that this occurs and data substantiating this contention are sparse and not convincing. Cross-sensitization with other derivatives of aminobenzoic acid may occur, but it is rare (Ref. 5).

(2) *Effectiveness.* The Panel concludes that tetracaine is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The un-ionized tetracaine base penetrates and stabilizes the axonal membrane and causes a blockage of the pain and other receptors in the skin. Tetracaine is much more lipid soluble than procaine and has 10 times the protein-binding capacity of procaine (Ref. 3). Tetracaine, therefore, has a longer latent period due to its slower penetration and diffusibility. It is two to four times longer lasting than procaine due to this greater lipid solubility and protein-binding effect. The duration of action is variable, as is the case with other local anesthetics and depends upon the site of application. This variability of duration from one area to another is due, to a great extent, to the differences in vascularity of the tissues. Tetracaine base and tetracaine salts are effective on the mucous membranes when applied topically (Ref. 5).

(3) *Evaluation.* The Panel concludes that tetracaine base is effective topically on the mucous membranes. However, due to the fact that serious and rapidly occurring fatal reactions due to systemic toxicity can occur when used by those not familiar with the hazards, the Panel recommends that it remain a prescription item for oral health care products and not be allowed for use in OTC products.

References

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

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

(3) Adriani, J., and D. Campbell, "Fatalities Following Topical Application of Local Anesthetics to Mucous Membranes," *Journal of the American Medical Association,* 162:1527–1530, 1956.

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

(5) OTC Volume 060047.

j. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is effective but not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is the salt of the tertiary amine tetracaine which has been described elsewhere in this document. (See part III. paragraph B.2.i. above—Tetracaine). Tetracaine hydrochloride consists of a white crystalline power that is odorless and hygroscopic. Tetracaine hydrochloride is soluble, 1 part in 7 parts of water, unlike

the base which is poorly water soluble. Tetracaine hydrochloride has a slightly bitter taste followed by a sense of numbness. Tetracaine hydrochloride melts between 147° and 150° C (Refs. 1 and 2).

Tetracaine hydrochloride hydrolyzes slowly and loses its anesthetic activity with time. The shelf-life of the powder in sealed ampulses is less than 1 year. The hydrochloride is the most widely used salt. Solutions of the hydrochloride salt are more stable than the base. The hydrochloride is converted to the base when injected or applied topically to the mucous membranes by the buffering mechanisms of the tissues, and for this reason the drug penetrates very rapidly into the blood stream (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that tetracaine hydrochloride is not safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is 10 times more potent and toxic than procaine (Ref. 1). It may be absorbed in large quantities from abraded and denuded areas since it is very water soluble. Tetracaine hydrochloride produces convulsions and cardiac depression similar to other local anesthetics (Ref. 5). Reactions of this type from topical application of tetracaine hydrochloride to the mucous membranes have been reported. Tetracaine hydrochloride manifests no appreciable degree of irritancy. The sensitizing potential is low, but, like all other anesthetics of its type, will cause allergic reactions. Tetracaine hydrochloride can act as a hapten and cause allergic reactions mediated by IgE immunoglobulins (Ref. 6). Repeated application can cause the cytotoxic type of sensitization mediated by the T-cell lymphocyte. Local reactions are characterized by rashes, aczema, etc. (Ref. 7).

(2) *Effectiveness.* The Panel concludes that tetracaine hydrochloride is effective as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

Tetracaine hydrochloride is highly ionized and does not readily penetrate lipid barriers of the cell membrane. Tetracaine hydrochloride is very slowly absorbed from the intact skin and, therefore, exerts no significant therapeutic effect (Refs. 4 and 8). Aqueous solutions are acidic (pH 5 to 6), but when injected into tissues or applied topically on the mucous membranes they are converted to the base, which is the physiologically active form. Tetracaine hydrochloride is effective when it comes into contact with the tissue fluids because it is converted to the base, the active form, penetrating the neuronal membrane and blocking conduction of nervous impulses.

(3) *Evaluation.* The Panel concludes that tetracaine hydrochloride is effective as a topical anesthetic/analgesic on the mucous membranes. Due to its potential for producing severe, obvious, and often fatal systemic reactions, however, it is not recommended for use in OTC products but should remain available by prescription.

References

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

(2) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 995–996, 1975.

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 99–106, 1973.

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

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

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

(7) OTC Volume 060047.

(8) Adriani, J., and H. Dalili, "Penetration of Local Anesthetics Through Epithelial Barriers," *Anesthesia and Analgesia,* 50:834–840, 1971.

Category II Labeling (Anesthetics/Analgesics)

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing anesthetic/analgesic active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action when it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Relieves dryness."

(2) "First aid for throat irritations."

(3) "Soothing to smokers throat."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms, that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Is quick comfort to irritated throats."

(2) "Fast acting local anesthetic action."

(3) Fast acting temporary relief of minor throat pain."

(4) "Fast temporary relief of minor sore throat pain."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior and fast acting relief of minor throat pain, cough, or colds."

(2) Adding such terms or "plus" etc.

d. *Statements or phrases that are vague in this meaning and cannot be readily understood or are misleading.* (1) "Soothes tired throats."

(2) "Is quick to comfort irritated throats."

(3) "For temporary relief of sore throat associated with colds and excessive smoking."

(4) "Promotes healing by protecting the affected area from further irritation (oral bandage)."

(5) "Clings tenaciously to oral tissue."

e. *Statements or phrases in the indications for uses that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "For temporary relief of pain associated with tonsillitis and pharyngitis."

(2) "For temporary relief of pain associated with canker sores."

(3) "Temporary relief of pain of stomatitis."

(4) "Relief of pain and discomfort in pharyngitis and throat infections."

(5) "Relieve minor throat pain and pain from aphthous ulcers (canker sores)."

(6) "For acute tonsillitis."

f. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Anesthetic."

(2) "Analgesic."

(3) "Liquid anesthetic for mouth and throat."

(4) "As a topical anesthetic."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

Eucalyptol
Methyl Salicylate
Thymol

a. *Eucalyptol.* The Panel concludes that eucalyptol is safe but that there are insufficient data available to permit

final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Eucalyptol is a volatile oil prepared by steam distillation of the fresh leaves of *Eucalyptus globulus* (Ref. 1). The eucalyptus tree is native to Australia, Tasmania, and the Malysian regions.

Eucalyptol is colorless, or a pale yellow volatile liquid with a characteristic aromatic, somewhat camphoraceous odor, and a spicy and cooling taste (Ref. 2). Its specific gravity is 0.905 and its refractive index is 1.458 to 1.470. Approximately 70 percent of eucalyptus oil is in the form of one of its active ingredients, namely, eucalyptol (Ref. 3). Eucalyptol is also known as cineol, cineolcayeptol, and cajuptol. It is insoluble in water, but it is miscible with alcohol, chloroform, and ether. Eucalyptus oil and eucalyptol have both been characterized as flavors in the "National Formulary." They both have feeble analgesic and antiseptic effects and both have been used as stimulatory expectorants and as vermifuges (Refs. 4 and 5).

The characteristic odor of eucalyptol is considered to be a "medicinal odor" by the users of OTC products, and it acts as a placebo. Eucalyptol has been used topically for the treatment of certain forms of skin diseases. It is an active germicide, but is not as effective as many other volatile oils (Ref. 2).

(1) *Safety.* The Panel concludes that eucalyptol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

If eucalyptol is taken internally in large quantities, toxic symptoms may occur. These symptoms include epigastric burning, nausea, vomiting, tachycardia, dizziness, muscular weakness, a feeling of suffocation, and in severe cases delirium and convulsions. Death has occurred in about one-third of the human subjects who ingested between 10 and 30 mL of the oil. Idiosyncrasy towards small doses may be manifested by skin eruptions (Refs. 6, 7, and 8). Sensitization to eucalyptol has been observed but is believed to occur infrequently (Refs. 6, 9, 10, and 11).

Jenner et al. (Ref. 12) found that the LD_{50} of eucalyptol for rats is 250 mg/kg. It is relatively safe when applied topically to the skin. Jori and Briatico (Ref. 13) studied the effects of administering eucalyptol subcutaneously to pregnant rats. It was noted that eucalyptus oil greatly increased the liver microsomal activity during and after pregnancy. It was also found that this increased activity was higher in the fetal and newborn offspring.

The question of carcinogenic activity of eucalyptol has been raised by several investigators (Refs. 14 and 15). Homburger (Ref. 15) found that eucalyptol applied to the skin of mice caused development of tumors in about 10 percent of the animals treated.

Marketing experience of a topical anesthetic product containing small amounts of eucalyptol produced no evidence of lack of safety (Refs. 16 and 17).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Historically, eucalyptus oil has been used as a stimulating expectorant and as a locally applied antiseptic with a very mild anesthetic effect. It has also been used as a vermifuge. Eucalyptol is a mild local irritant that is used as an inhalant, especially in bronchitis. It can be administered by inhalation by adding a teaspoonful to hot water and vaporizing the water. It can be given internally by placing 5 to 10 drops on sugar. Eucalyptol is used in the treatment of the "common cold"; sprays of 3 to 5 percent solutions in liquid petrolatum have been used. The usual dose is 0.3 mL.

The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in the **Federal Register** of September 9, 1976 (41 FR 38347) has written a great deal on the antitussive effects of eucalyptol in various currently marketed OTC topically applied preparations consisting of ointments, liquids, and tablets. The conclusions of this Panel support the conclusions discussed above; namely, eucalyptol has no analgesic effect and does not interfere with the reflex arc involved in completion of the cough reflex resulting from local stimulus in the pharynx. The data submitted consisted of combinations of volatile oils that included eucalyptol as one of the ingredients. Data were submitted concerning the effectiveness of the ingredient alone.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025- to 0.1-percent concentration of eucalyptol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 1 to 30 mg of eucalyptol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetics/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 561–564, 1955.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 1950 Ed., J. B. Lippincott Co., Philadelphia, pp. 458–460, 1950.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 147, 1948.

(4) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 517, 1973.

(5) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1230, 1975.

(6) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 169, 1957.

(7) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 169, 1975.

(8) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 653, 1968.

(9) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 379, 1973.

(10) Sayre, R. M., et al., "The Correlation of Indoor Solar Simulator and Natural Sunlight: Testing of a Sunscreen Preparation," *Archives of Dermatology,* 114:1649–1651, 1978.

(11) Samitz, M. H., and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *Cutis,* 5:180–185, 1969.

(12) Jenner, P. M., et al., "Food Flavourings and Compounds of Related Structure: I. Acute Oral Toxicity," *Food and Cosmetics Toxicology,* 2:327–343, 1964.

(13) Jori, A., and G. Briatico, "Effect of Eucalyptol on Microsomal Enzyme Activity of Foetal and Newborn Rats," *Bicochemical Pharmacology,* 22:543–544, 1973.

(14) Roe, F. J. C., and W. E. H. Field, "Chronic Toxicity of Essential Oils and

Certain Other Products of Natural Origin," *Food and Cosmetics Toxicology,* 3:311–324, 1965.

(15) Homburger, F., and E. Boger, "The Carcinogenicity of Essential Oils, Flavors, and Spices: A Review," *Cancer Research,* 28:2372–2374, 1968.

(16) OTC Volume 060013.

(17) OTC Volume 060014.

b. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Methyl salicylate is the methyl ester of salicylic acid which is made by esterifying methyl alcohol with salicylic acid. One milliliter methyl salicylate has a salicylate content equivalent to 1.4 g aspirin. Methyl salicylate is a volatile liquid having a density of 1.18 g/mL. At low concentrations, it is employed as an organoleptic agent for both its condimental flavor and pleasing aroma. Methyl salicylate has a counterirritant action for temporary relief of deep-seated pain when applied to the skin (Refs. 1 through 5).

Methyl salicylate penetrates the intact skin and is absorbed into the system circulation. It is also readily absorbed from the mucous membranes. Some data are available indicating that the amounts absorbed percutaneously are sufficient to have significant anesthetic activity (Refs. 6 through 9). Methyl salicylate has been used on the mucous membranes to obtain systemic effects. There are no data to substantiate that methyl salicylate blocks nerve conduction as do topical anesthetics, such as benzocaine.

Prior to the discovery of a method for chemical synthesis of methyl salicylate, it was produced by steam distillation from natural sources. The natural-source products are known as gaultheria oil, betula oil, sweet birch oil, teaberry oil, and wintergreen oil. Today, these names are used synonymously with methyl salicylate. Methyl salicylate is prepared synthetically by esterifying salicylic acid with methanol.

(1) *Safety.* The Panel concludes that methyl salicylate is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has given much consideration to the question of toxicity of methyl salicylate. The association of the odor of methyl salicylate with the odor of candy (wintergreen and teaberry flavors) has been linked by the American Medical Association to the ingestion by children of drug products containing more than therapeutic and safe amounts of methyl salicylate (Ref. 10). However, the National Clearing House of Poison Control Centers, Bethesda, Maryland, reviewed reports of poisoning due to ingestion of methyl salicylate, primarily in ointment formulations, which revealed no deaths and few cases with severe symptoms from 1970 to 1972. Recent regulations requiring the use of child-resistant containers for liquid preparations containing more than 5 percent methyl salicylate (16 CFR 1700.14(a)(3)) provide an important safeguard for small children, who have constituted a large percentage of the victims of accidental poisoning from drinking poisonous substances.

Except for severe local irritations of the mucous membranes, ingested methyl salicylate is not notably different in its toxic actions from other salicylates. Metabolic acidosis may be a more prominent complication of salicylate overdosage with the methyl ester than with other derivatives of salicylic acid (Ref. 11). The average lethal dose of methyl salicylate is approximately 10 mL for children and 30 mL for adults (Refs. 12 and 13). However, the ingestion of as little as 4 mL (4.7 g) methyl salicylate has caused fatalities in children (Ref. 14). For comparative purposes, it should be noted that the salicylate content of 4 mL (4.7 g) methyl salicylate is equivalent to 4.3 g salicylic acid, 4.96 g sodium salicylate, or 5.6 g aspirin. Death has ensued following ingestion of 3 g salicylic acid and 4 g sodium salicylate (Ref. 15). The toxic dose of aspirin is in the range of 75 to 150 mg/kg. This is equivalent to 5.3 to 10.5 g for a 154-lb adult. Methyl salicylate is generally recognized as safe (GRAS) in candy at 0.03 percent and GRAS in chewing gum at 0.33 percent.

There is adequate evidence to support the contention that ingestion of more than small condimental amounts of methyl salicylate is hazardous. However, the concentrations of methyl salicylate contained in marketed oral health care products reviewed by the Panel are within a range which the Panel considers safe for OTC use on the mucous membranes of the mouth and throat. The Panel does recommend, in the interest of safety, that a maximum concentration of 0.4 percent be used.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat.

The amount of salicylate absorbed following topical application of methyl salicylate is unpredictable. There are insufficient data to support the contention that salicylates stabilize the neuronal membrane as do topical anesthetics such as benzocaine or tetracaine. Conclusions that it is an anesthetic have been based largely upon the assumption that blood levels of topically administered salicylates must be of the same order as "effective blood levels" associated with orally administered salicylates. Lim and co-workers (Ref. 16) have observed that salicylates elicit their anesthetic effects peripherally, not centrally, and block pain by direct action on pain receptors by inducing an anti-inflammatory action. Recent advances in knowledge regarding the supposed role of prostaglandins causing pain syndromes and the ability of salicylates to inhibit the biosynthesis of prostaglandins may shed further light upon the role of salicylates applied topically to relieve locally painful symptoms. It has not been established that methyl salicylate applied to the mucous membranes plays any such role.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to a 0.4-percent concentration of methyl salicylate in the form of a rinse, mouthwash, gargle, or spray, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetics/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Krantz, J. C., and D. J. Carr, "The Pharmacologic Principles of Medical Practice," 6th Ed., Williams and Wilkins, Baltimore, p. 200, 1965.

(2) Woodbury, D. M., and E. Fingl, "Analgesic-Antipyretics, Anti-inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 335, 1975.

(3) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 562–563, 1970.

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

(5) Boyd, E. M., "Antitussives, Antiemetics, and Dermatomucosal Agents," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J. R. DiPalma, McGraw-Hill Book Co., New York, p. 1036, 1971.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 749–750, 1973.

(7) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Adsorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 987–1001, 1970.

(8) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, p. 560, 1970.

(9) Beutner, R., et al., "On the Absorption and Excretion of Methylsalicylate Administered by Inunction," *The Journal of Laboratory and Clinical Medicine,* 28:1655–1663, 1943.

(10) Conley, B. E., et al., "Candy Medication and Accidental Poisoning," *Journal of the American Medical Association,* 158:44–45, 1955.

(11) Davison, C., E. F. Zimmerman, and P. K. Smith, "On the Metabolism and Toxicity of Methyl Salicylate," *Journal of Pharmacology and Experimental Therapeutics,* 132:207–211, 1961.

(12) Deichmann, W. B., and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 662, 1969.

(13) Soine, T. O., and R. E. Willette, "Analgesic Agents," *in* "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 5th Ed., edited by C. O. Wilson, O. Gisvold, and R. F. Doerge, J. B. Lippincott Co., Philadelphia, p. 675, 1966.

(14) Beckman, H., "The Year Book of Drug Therapy—1969," Year Book Medical Publishers, Chicago, p. 268, 1969.

(15) Thienes, C. H., and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 80, 1972.

(16) Lim, R. K. S., et al., "Site of Action of Narcotic and Non-narcotic Analgesics Determined by Blocking Bradykinin-Evoked Visceral Pain," *Archives Internationales de Pharmacodynamie et de Therapie,* 152:25–58, 1964.

c. *Thymol.* The Panel concludes that thymol is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol, also known as thyme camphor, is 5-methyl-2-isopropyl-1-phenol. It may be prepared synthetically or obtained from volatile oils distilled from *Thymus vulgaris* and other related plant sources. Thymol occurs as colorless crystals which are often large, or as a white crystalline powder. It melts at 51° C and boils at 233° C. One gram dissolves in 1 liter (L) of water. It is highly soluble in alcohol, chloroform, and in mineral and other volatile oils (Ref. 1). Thymol has a characteristic aromatic thyme-like odor and a pungent taste. It has appreciable volatility and can be administered with steam or in water vapor when prepared in an aqueous solution. Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 2). Its antimicrobial effects have been described elsewhere in this document. (See part IV. paragraph B.3.w. below—Thymol.)

(1) *Safety.* The Panel concludes that thymol is safe as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol has a pleasant, aromatic odor. It is sometimes referred to as a volatile or essential oil. Thymol has been used for a variety of medicinal purposes but has, in many cases, fallen into disuse and been supplanted by newer, more effective drugs. It has been incorporated into mouthwashes for its antiseptic action and as a flavorant. Thymol has been used topically and orally as an antifungal agent for the treatment of actinomycosis. It also has been used internally as an intestinal antiseptic and anthelmintic, especially against hookworm (Refs. 3 and 4).

The intravenous LD_{50} of thymol in mice is 74 mg/kg (Ref. 5). Jenner (Ref. 6) studied the acute oral toxicity of thymol instilled into the stomach by intubation in the rat and guinea pig. The LD_{50} for the rat was 980 mg/kg and for the guinea pig, 880 mg/kg.

Chronic toxicity was observed in 5 male and 4 female rats given an oral dose of 10,000 parts per million for 19 weeks. No untoward effects were noted after this period of time (Ref. 7).

Oral ingestion of 1 g thymol usually does not cause any adverse symptoms except the feeling of warmth in the stomach. According to Sollman (Ref. 4):

> Larger doses [than 1 g] produce dizziness, severe epigastric pain, excitement, soon followed by nausea, vomiting, marked weakness, drowsiness, quick soft pulse, tinnitus and deafness, salivation, sweating; then collapse with cyanosis, fainting, coma, low temperature, slowed pulse and respiration. Abortion may result. Rashes are not uncommon.

A report by Barnes (Ref. 8) noted that over 1,000,000 doses of thymol averaging 1 g per dose resulted in reported deaths of 20 debilitated patients.

Samitz and Shmunes (Ref. 9) noted that dentists and other allied personnel found thymol one of the less frequent sensitizers in occupational dermatoses. Thymol irritates the mucous membranes, but when topically applied to the skin it has little effect and is virtually unabsorbed (Ref. 4). The oral toxicity of thymol is about one-fourth that of phenol and, if it is absorbed, one-half is metabolized totally. The remainder is conjugated with sulfuric acid and glucuronic acid and excreted into the urine (Ref. 4).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol as an OTC anesthetic/analgesic active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol was first introduced as a disinfectant. It has a phenol coefficient of 27.6, but its activity is greatly reduced by the presence of proteins. It also has some antiviral activity (Ref. 10). In 1891 Potter (Ref. 11) stated that thymol was a topical anesthetic when used on the skin and mucous membranes. Buckley (Ref. 12) also noted that thymol had topical analgesic properties and was considered superior to phenol as an antiseptic.

The Panel concedes that it is possible that thymol is an anesthetic when topically used on the mucous membranes of the oral cavity because of its phenolic nature, but it does not have sufficient evidence and documentation supporting this claim. Most of the literature reveiwed on the subject refers to thymol's antimicrobial and antifungal effects. Although 1 to 2 percent concentrations of thymol have been used clinically for topical analgesia, there is insufficient evidence as to the effectiveness of such concentrations.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.006- to 0.1-percent concentration of thymol in the form of rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 0.2 to 15.0 mg of thymol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervison of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care anesthetic/

analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evalution.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anesthetic/analgesics. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1189–1190, 1973.

(2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 2d Ed., The Macmillan Co., New York, p. 1082, 1960.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1191, 1970.

(4) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicoloy," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227–228, 1957.

(5) Edwards, E. H., and B. Hall, "Thymol as a Bacteriostatic Agent," *The Pharmaceutical Journal,* 166:54, 1951.

(6) Jenner, P. M., et al., "Food Flavourings and Compounds of Related Structure: I. Acute Oral Toxicity," *Food and Cosmetic Toxicology,* 2:327–343, 1964.

(7) Hagan, E. C., et al., "Food Flavourings and Compounds of Related Structure: II. Subacute and Chronic Toxicity," *Food and Cosmetics Toxicology,* 5:141–157, 1967.

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

(9) Samitz, M. H., and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *Cutis,* 5:180–185, 1969.

(10) Dunham, W. B., and W. J. MacNeal, "Culture on the Chick Chorio-allantois as a Test of Inactivation of Vaccinia Virus," *Journal of Bacteriology,* 44:413–424, 1942.

(11) Potter, S. O. L., "Handbook of Materia Medica, Pharmacology, and Therapeutics," 3d Ed., P. Blakiston, Son and Co., pp. 389–390, 1891.

(12) Buckley, J. P., "Modern Dental Materia Medica, Pharmacology and Therapeutics," 5th Ed., P. Blakiston's Son and Co., Philadelphia, pp. 48, 60, and 515, 1926.

Category III Labeling

None.

C. Data Required for Evaluation

The Panel agrees that the protocols recommended in this document for studies required to bring a Category III drug into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing topical anesthetics/analgesics for use in the oral cavity.* The effectiveness of topical anesthetics/analgesics should be determined by their ability to obtund or relieve the pain and discomfort due to acute or chronic pathologic states of the mouth and throat. The Panel recognizes that there are no established protocols for testing the effectiveness of this category of product by using objective methods and that all testing is, by and large, subjective. Tests can be made on patients who have pain or on volunteers in whom pain can be induced experimentally. All tests should involve a double-blind, placebo-controlled assessment of the ability of the drug to decrease pain due to sore mouth and sore throat.

The data should be obtained using the same drug that is present in the OTC preparation. It should be used in the same dosage and applied in the same manner recommended in the instructions in the labeling of the preparation. Since anesthetics/analgesics may be administered repeatedly during episodes of pain, dosing should be at appropriate times necessary to maintain optimal relief of symptoms. Data should also be obtained by testing the topical anesthetics/analgesics in recommended concentrations and at maximal dosage frequencies for periods of at least 5 days. This must be done in order to assess both its sustained effect and the potential for inducing irritancy or allergenicity.

Volunteers without pain may be tested using an established method of algesimetry such as that of Adriani and Zepernick (Ref. 1) which utilizes an electrical current applied to the tip of the tongue as a painful stimulus. Nebulized solutions of citric acid may also be used, particularly when obtaining data substantiating a cough claim.

2. *Selection of patients.* Selection of patients for testing should be based on the cause and established diagnosis of sore mouth or sore throat. Patients with chronic conditions causing sore mouth or sore throat usually present relatively stable conditions; consequently, subjects of this type may be selected for a cross-over, double-blind study. Such subjects can serve as their own controls. Subjects without pain being tested using algesimetric methods of assessment may be tested in this manner also. Patients with acute infections, or conditions that induce pain in the mouth and throat represent a larger portion of a patient type to self-medicate with a topical anesthetics/analgesics. Because of the relatively brief duration of these acute disorders and greater variation in type and intensity of the pain or discomfort and stability of the lesion causing the pain, a greater number of patients should be studied than when the cross-over, double-blind technique is used. They should be studied by assigning them in random fashion into two groups, a placebo group and a drug group. The placebo should be indistinguishable from the drug being tested. Each should be of equal size. Further, for comparative purposes, all groups must be matched by age, sex, and, if possible with the exception of the volunteers, the degree of pain at the time of the study.

3. *Methods of study.* Observations should include subjective response on patients with pain and the responses measuring the anesthetic/analgesic effect by a technique of algesimetry. The technique employed by Adriani and Zepernick (Ref. 1) described above, using electrical current applied to the tongue is acceptable to the Panel and has been widely used in evaluations of effectiveness of topical anesthetics/analgesics on the mucous membranes. Individual patient diaries should be kept in which is recorded all pertinent data such as date, times of testing, onset and duration of pain relief, dose, etc. Observation should include the time of onset, magnitude, and duration of the response. A scoring technique evaluating the effectiveness of the drug in relieving pain, such as indicating the response as 0 for no effect, 1 for poor, 2 for fair, 3 for good, and 4 for excellent can be used.

4. *Interpretation of the data.* The recommended dose for the test drug should induce a statistically significant reduction in mouth and throat pain when compared with a placebo response.

Evidence of a drug's effectiveness is required from 25 subjects with chronic pain and 25 volunteers. Subjects should be from a target population for whom the drug is intended to be used. Studies involving patients with acute pathologic states for whom no baseline can be obtained should include 75 to 100 subjects. A minimum of three different investigators or laboratories must be used.

All data submitted to the FDA must present both favorable and unfavorable results.

5. *Evaluation of safety.* Tests of safety should involve usual tests for acute and chronic toxicity relative to the known possible adverse effects of drugs described previously. (See part II. paragraph C.2. above—Testing for recategorization of Category III

ingredients.) Tests should be done and dose response curves be established for acute toxic effects utilizing the dose range from minimum effectiveness dose up to a maximum therapeutic effectiveness.

Reference

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

IV. Antimicrobial Agents

A. General Discussion

The Panel disagreed on important issues relevant to the safety and effectiveness of antimicrobial agents and also on the types of testing methodologies to be included in the data required for evaluation of antimicrobial agents. Accordingly part IV.—Antimicrobial Agents consists of a majority report and a minority report. The minority report reflects the opinion of one Panel member.

1. *General comments.* Topical antimicrobial ingredients are applied to the mucous membranes of the mouth and throat to kill, inhibit the proliferation of, or alter the metabolic activity of all types of microorganisms, both pathogenic and non-pathogenic. This process is called "antiseptics"; agents that are used for this purpose are called "antisepsis." The term "antiseptic" implies that some therapeutic benefit results when such agents are used. Antiseptics are used in an attempt to sterilize intact cutaneous and mucous surfaces, contaminated or infected wounds, mucosal ulcerations, or other lesions caused by pathogenic microbial activity. There is considerable evidence indicating that these agents are not only ineffective but may also retard the healing of clean or infected wounds.

There is an abundance of documentation, both in older and more recent authoritative texts written by authorities on microbiology, which states that the topical application of antiseptics is of doubtful therapeutic value.

Grollman and Slaughter (Ref. 1) states as follows:

A very large number of substances possess disinfectant properties, that is, are capable of destroying microbes when they can be applied in sufficient quantity. They have no specific action on the microbes, however, but act as general protoplasmic poisons, destroying living tissue of all kinds wherever they come in contact with it. On the other hand, drugs such as strychnine, which act on specialized parts of the vertebrate organism and have less effect on the less differentiated tissues, are equally harmless to the undifferentiated protoplasm of the microbes. It is of importance to note that the ordinary antiseptics do not act more strongly on microbes than on the tissues in which they are embedded or on the phagocytes with which the organism is combating the infection. The destruction of the septic organisms in a wounded surface entails the destruction of the surrounding cells also. Thus disinfection can only be carried out in a part in which the superficial cells are not of vital importance and may be restored by new growth. It is therefore impossible to disinfect the tissues of the body as a whole unless a drug is parasitotropic, that is, has a specific affinity for the parasite rather than for the organs in general (organotropic). Although many attempts were made to find drugs manifesting such selectivity it was only with the introduction of the sulfonamides, antibiotics and other systemic anti-infectives that this goal was attained. By the local or systemic application of these substances antisepsis may be obtained without injury to the normal tissues. The term antiseptic is now usually limited to the drugs exerting a local anti-infective action although in its broad sense it should also include the systemic anti-infectives described in previous sections.

* * * If microbes were confined to the surface, the latter would be sufficient for their destruction, but in order to disinfect a wound it is necessary to penetrate more deeply and thus efficient disinfection implies a certain amount of destruction to the tissues in which the microbes are harbored. This local destruction of cells and nervous structures induces pain and irritation and many efficient disinfectants are irritants. There action as irritants arises from the same qualities as their disinfectant power, namely, from their general toxicity to living matter.

When a surface has been poisoned by means of disinfectants, it heals less quickly, and this had led to the more sparing use of antiseptics and to the development of the aseptic method, in which organisms are excluded instead of being admitted and then destroyed. With the discovery of the sulfonamides and antibiotics these, in turn, displaced the previously used antiseptics in many cases for these substances not only inhibit the growth of the invading pathogens but induce only minimal or no injury to the normal tissues.

In addition to their local effect, many of the antiseptic and disinfectant drugs have a further poisonous action when they are absorbed and circulate in the blood, and this has led to a further limitation of their use. This general action does not necessarily arise from the qualities which render them antiseptic, and may be avoided by care in the choice of the drug and in its use.

Sollmann (Ref. 2) states as follows:

The field of antiseptics has become considerably restricted since they were introduced by Lister. They can be highly effective outside the body but they rarely penetrate sufficiently to kill bacteria in living tissues. When they do penetrate they are generally more effective in killing tissue cells than the bacteria. They do not really disinfect the tissues but may kill and embalm the bacteria on the surface.

Goth (Ref. 3) states as follows:

Prior to the discovery of chemotherapeutic agents, there was much preoccupation in synthesizing new compounds that could kill bacteria rapidly in high dilutions. The new antiseptics were generally compared with phenol and the ratio of the dilution that was necessary for killing test organisms in vitro was called the phenol coefficient. These efforts were so successful that antiseptics were synthesized that were 100 times more potent than phenol in killing bacteria in less than 10 minutes.

In retrospect much of this effort was misdirected. Any drug that can kill bacteria in a few minutes is bound to have a toxic effect on mammalian tissues. It is not surprising that even the most potent antiseptics were completely incapable of curing a systemic bacterial infection because the testing methods used for their development were designed for potency and not a favorable therapeutic effect. The discoverers of Prontonsil decided to test every compound against systemic infection in mice. The sulphonamides and penicillin would never have been discovered by testing methods, such as the use of the phenol coefficient. Not only the phenol coefficient but all the tools for evaluation of antiseptics are poor. It is not surprising that the field is dominated by empiricism and is greatly influenced by fashion.

Esplin (Ref. 4) states:

No group of drugs is employed more widely than the antiseptics and disinfectants. Among the agents discussed in this chapter are those germicides that are the most useful; however, some agents are mentioned not because they are particularly efficacious but because they are widely used.

The concept that infectious diseases are spread by microorganisms, at first so reluctantly accepted by the medical profession, is now embraced by the layman with an enthusiasm that is exceeded in degree only by ignorance. Each decade has seen advances in the discriminate and scientific use of disinfectants in reducing dissemination of pathogenic microorganisms and in the control of systemic and local infections by antibiotics and antiseptics. Nevertheless, the layman frequently employs the readily available germicidal agents in a ritual manner that rarely produces substantial benefit and often results in serious harm.

But the layman does not acquire this ritual instinctively nor does he follow it without persuasion. Those who profit from the promotion of germicidal preparations use the most advanced technics in the advertising media to induce the uniformed to purchase, through fear of infection, preparations that are usually costly, often worthless, and sometimes dangerous. The insecure layman is offered germicidal solutions, sprays, powders, and ointments for application to every surface and orifice of the body. The germophobia that drives him to this needless expense is entirely inappropriate to the present age. Information more directly serving the interests of public health would instruct in the rational prevention and

treatment of infectious disease. This "information gap" is illustrated by the common practice of using ineffective antiseptics in wounds, cuts, and abrasions in the mistaken belief that they reduce the chance of acquiring tetanus, a disease that is entirely preventable by proper immunization.

Nevertheless, there are indispensable uses of disinfectants in the household, in hospital sanitation, and in public health measures. Likewise, antiseptics find many legitimate therapeutic applications. The extent of use of antiseptics in therapy of local infections has declined with the increasing number of antibiotics and other systemic chemotherapeutic agents available. In spite of this fact, antiseptics are sometimes still of value in treating local infections caused by microorganisms refractory to systemic chemotherapy. It is the problem of the physician to choose wisely from the vast number of available drugs and to delineate the beneficial and the harmful uses of germicides.

Esplin (Ref. 4) further states as follows:

* * * Among the first uses of antiseptics in medicine were the treatment of wounds. It is now apparent that most germicides are of little value for this purpose due to their poor penetration into foci of infection, relatively low efficacy in body fluids, and their propensity for causing local tissue damage. They cannot be relied upon to prevent infection from bacterial contaminants, and they are, in general, markedly inferior to systemic chemotherapeutic agents in controlling an infection once it has developed. In the hands of experienced surgeons, selected germicides may be useful in cleansing wounds and in reducing bacterial contamination. However, the common belief that the substantial benefit is obtained from the application of antiseptics to wounds, cuts, and abrasions is not supported by the considerable evidence in this field. The various applications of surgical antiseptics have been considered in detail by Price (1968). [Price, P. B., "Surgical Antiseptics," *in* "Disinfection, Sterilization, and Preservation," edited by C. A. Lawrence and S. S. Block, Lea and Febiger, Philadelphia, pp. 401–429, 1968.]

The majority of local infections respond more dramatically to appropriate chemotherapeutic drugs administered systemically than to antiseptics. Antiseptics are sometimes useful in treating infections caused by microorganisms that are unaffected by chemotherapeutic drugs, through the development of drug resistance or otherwise. In refractory infections, antiseptics are occasionally employed in conjunction with systemic chemotherapeutic agents. Furthermore, germicidal drugs are useful in the prophylaxis against specific infections.

Jawetz, Melnick, and Adelberg (Ref. 5) state as follows:

Disinfectants. Disinfectants and antiseptics differ from systemic reactive antimicrobials in that they possess little selective toxicity. They are toxic not only for microbial parasites but for host cells as well; therefore, they can be used only to inactivate microorganisms in the inanimate environment or to a limited extent on skin surfaces but they cannot be administered systemically and are not active in tissues.

Modell, Schild, and Wilson (Ref. 6) state as follows:

The number of disinfectants and antiseptics used is large because there is no such thing as an ideal disinfectant. The properties required vary widely, according to the manner in which the drug is intended to be used. The intensity and speed with which a drug kills bacteria can be measured in a test tube, and this information is of great value for determining, for example, the relative efficiency of disinfectants when applied to inorganic material. Such measurements give little indication of the relative values of disinfectants when applied to living tissues, because in this case the important issue is whether the substance that will kill or at least prevent the multiplication of bacteria will not also injure the surrounding tissues. Indeed, some of the best antiseptics for the treatment of wounds are substances which have a relatively feeble and slow action in vitro, and there are authoritative opinions that beyond their mechanical effects of removing debris and soil they accomplish little.

Banovetz (Ref. 7) states:

Topical Medication for the Throat. Definitive topical treatment of pharyngeal disease is not possible except in monilial infections for which nystatin is used. For the most part treatment is symptomatic. Patients feeling better will continue treatment but the critical physician must regard this as art, and not science. Painting sore throats with 2% silver nitrate or Mandel's solution (iodine) is comforting but not antibacterial.

Medical troches do not deliver drugs below the epithelial surfaces but they may have some surface cleansing action.

Although silver nitrate is not an ingredient considered by the Panel for OTC use, it is a topical antiseptic. Iodine has been considered by this Panel for topical use to treat sore throat and sore mouth.

Harvey (Ref. 8) states:

Antiseptics and disinfectants are employed very widely and are thus deserving of sober consideration.

Once the germ theory of disease was accepted by the medical profession and antisepsis by chemical agents was demonstrated scientifically, topical antimicrobial drugs were employed with naive enthusiasm by both physicians and laymen. Astute physicians early learned the limitations of antiseptics, but the vast majority of physicians and laymen alike employed such drugs uncritically and often inappropriately, encouraged by promotional propaganda almost from the very beginning. Although several effective and useful antiseptics, such as iodine, were known quite early, in the first half of this century there was a rush to accept a host of lesser and even useless drugs. The euphoria surrounding the discovery of the sulfonamides and antibiotics obscured the need for a thoroughgoing appraisal of the value of antiseptics, collectively and individually. Only a few of the antiseptics have been subjected to controlled clinical comparison with other agents, and clinical standards have yet to be accepted. Both laymen and many physicians still continue to employ the topical antimicrobial drugs in a ritual manner that is often irrational, usually ineffective, and occasionally harmful.

Nevertheless, there are indispensable uses of disinfectants in the household, in hospital sanitation, and in public health measures. Likewise, antiseptics find many legitimate therapeutic applications. Even though systemic antimicrobial drugs have quite properly caused a decline in the use of topical anti-infective agents, antiseptics are sometimes still of value in treating local infections caused by microorganisms refractory to systemic chemotherapy and in the supplementation of such therapy. It is the problem of the physician to choose wisely from the vast number of available drugs and to delineate the beneficial and the harmful uses of germicides.

In this chapter [of "The Pharmacological Basis of Therapeutics"], a drug may receive special attention because of its undoubted efficacy, its toxicity, or the need to deflate an undeserved status.

Sanders and Sanders (Ref. 9) state as follows:

Antibacterial agents may adversely affect the host either directly or indirectly. Direct injury, or toxicity, is the focal point of this review. Indirect injury may result from (a) induction of an allergic or hypersensitivity reaction in which components of the immune system (antibody, activated cells, complement) mediate damage to host tissues or (b) alteration of the ecological balance of the normal microbial flora which facilitates superinfection or impairs epithelial physiology or nutrition.

Many clinicians consider the application of antiseptic solutions to contaminated wounds, ulcerations, or other lesions due to, microbial activity an unphysiologic procedure of doubtful value, and they feel that their use can be harmful. Therefore, they recommended that antiseptics not be applied to clean wounds or lesions resulting from microbial activity. Careful cleansing or irrigation of wounds and ulcerations and removal of foreign material from ulcerated surfaces by mechanical means, such as swabbing, irrigation, or use of sprays to assure free drainage, are considered more effective and less likely to injure tissues.

Most antiseptics harm both the microorganism and cells of the host. They cannot be used systemically. Except for use on the skin, they are of limited value. The introduction of anti-infective drugs such as the chemotherapeutic agents, antibiotics,

and other drugs possessing selective toxicity for particular microorganisms or classes of pathogenic microorganisms without harming the cells of the host, has caused relegation of most antiseptics for use in the mouth and throat into obsolescense. It is the consensus of the Panel that the term "oral antiseptic" not be used.

Despite these well-known concepts concerning the possible adverse effects of antiseptic agents, the practice of using these agents to attempt to relieve symptoms due to infections or to accelerate wound healing is so ingrained in the minds of both consumers and health professionals alike that attempting to discourage their use appears to be futile. In addition, the promotional practices of manufacturers of OTC products encourage rather than discourage self-medication with these products.

The ideal antiseptic should destroy all types of bacteria, fungi, viruses, and other infective organisms without harming the living tissues of the host. None, however, have been demonstrated to have this attribute, and some healthy cells are invariably injured. All effective antiseptics are general protoplasmic poisons and most have limited and varying spectra of antimicrobial activity which also limit their usefulness.

Antiseptics and antisepsis must be distinguished from disinfectants and disinfection. Disinfectants are used on inanimate objects to destroy microorganisms that are in the nonsporing state. Some disinfectants, such as phenol and the quaternary nitrogenous compounds, can be used as antiseptics if they can be diluted sufficiently to minimize injury to living tissues without loss of antimicrobial activity. Other antimicrobial agents are not suitable as antiseptics, particularly in the mouth and throat. They may require prolonged contact to be effective and this is usually difficult to achieve on oral mucosa. Futhermore, prolonged contact increases the likelihood of simultaneous injury to the pathogenic organisms as well as to the cells of the host. Sterilization is the complete and total destruction of all microbial life, including bacterial spores, vegetating bacteria, viruses, and fungi. Any agent that does not cause total destruction of microorganisms is a disinfectant when used on an inanimate object and an antiseptic when used on living tissues. The term "sanitize" is used to denote the reduction of bacterial flora on inanimate objects to an acceptable level that reduces the chance of infections. These terms are often confused, used erroneously, and sometimes interchangeably.

In summary, an "antimicrobial agent" kills or interferes with the proliferation and activity of many microorganisms, both pathogenic or non-pathogenic. A therapeutic benefit may or may not be derived from its use. An "antiseptic" is an antimicrobial agent which, when used on living tissues, produces some therapeutic benefit and acts to counteract an infection. A "disinfectant" is an antimicrobial agent used on inanimate objects to kill all types of microorganisms that are in the nonsporing state. A "sanitizing agent" is an antimicrobial agent that reduces bacterial flora on inanimate objects to a level that reduces the possibility of infections.

The virucidal effects of many antimicrobial agents have not been established with certainty. Many agents that kill bacteria, fungi, or other pathogenic organisms do not kill viruses.

References

(1) Grollman, A., D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 772–773, 1947.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed. W. B. Saunders Co., Philadelphia, p. 568, 1948.

(3) Goth, A., "Medical Pharmacology: Principles and Concepts," 6th Ed., C. V. Mosby Co., St. Louis, P. 578, 1972.

(4) Esplin, D. W., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 1032–1034, 1970.

(5) Jawetz, E., J., L. Melinick, and E. A. Adelberg, "Review of Medical Microbiology," 12th Ed., Lange Medical Publications, Los Altos, CA, p. 118, 1978.

(6) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, p. 692, 1976.

(7) Banovetz, J. D., "Topical Drugs—Basic and Applied," *in* "Otolaryngology: Volume 1. Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shmrick, W. B. Saunders Co., Philadelphia, p. 463, 1973.

(8) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides, " *in* "The Parmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 987, 1975.

(9) Sanders, W. E., and C. C. Sanders, "Toxicity of Antibacterial Agents: Mechanism of Action on Mammalian Cells," *Annual Reviews of Pharmacology and Toxicology, 19:53–83, 1979.*

2. *Antimicrobial agents for use in the oral cavity.* The most widely used antimicrobal agents in OTC oral health care drug products are aliphatic alcohols, aromatic alcohols (phenolic compounds), elemental and organic iodine preparations, organic derivatives of mercury, preparations containing aluminum, zinc, or chromium, cationic agents such as quaternary nitrogenous compounds, anionic agents such as detergents and soaps, boric acid and other boron derivatives, chelating agents such as oxyquinoline, and oxidizing agents such as the peroxides. Various balsams, tars, and aromatic bodies, often referred to as volatile (essential) oils, have been used as antimicrobial agents since earliest antiquity. A general discussion of the chemical nature and therapeutic effectiveness of these agents appears below.

The ideal antimicrobial agent should possess selective toxicity, that is, it should kill or permanently inhibit the activity of pathogenic organisms without causing injury to the cells of the host harboring the pathogen. None of the antimicrobial agents used in OTC oral health care products have been demonstrated to possess this attribute. The antibiotics and various chemotherapeutic agents come closest to attaining this attribute. These, however, are not available to consumers as OTC products because the diagnosis of the clinical conditions requiring their use, determination of appropriate dosage, and the selection of the proper antimicrobial agent must be done by a dentist or physician. Furthermore, they act systemically and must be administered orally or parenterally so that they can circulate in the blood and reach the infected areas via that route.

It is the consensus of the Panel that the effective use of antimicrobial agents in OTC products for self-medication and relief of symptoms due to infections of the mouth and throat caused by pathogenic organisms has not been convincingly demonstrated. The use of these antimicrobial active ingredients appears to be unwarranted, and there is evidence that they may be harmful in some instances. The Panel recognizes that antiseptics have widespread acceptance by the lay consumer even though indisputable evidence of their effectiveness has not been documented by controlled studies or proven to be of benefit from widespread clinical experience. The Panel, therefore, feels obligated to discourage the use of antimicrobial agents in oral health care products and recommends only those that are proven to be safe and effective and can be used properly for self-medication.

The Panel concludes that there are a number of valid reasons for advocating that antimicrobial agents not be used for therapeutic purposes in OTC oral health

care preparations. First, the Panel believes that the consumer is unable to determine the identity of organisms causing the symptoms requiring treatment and would not be able to exercise proper judgement in selecting the correct agent, even if the nature of the microorganism were known. Second, topically applied antiseptics act superficially on the surface of a lesion and do not necessarily penetrate deeply into the tissues at the site of action of an inflammatory process. Thus, only the microorganisms on the mucosal surface are killed, while those deep in an inflammatory process are untouched. Third, antiseptics may also kill indigenous oral microorganisms which maintain a delicate balance between the nonpathogenic and pathogenic microbial population of the mouth. Fourth, the action of antimicrobial agent has been diluted or eliminate by salivation and swallowing, the growth of the organism resumes. Fifth, antimicrobial agents may lead to development of resistant strains of pathogens that persist in the mouth and throat and kill or injure some of the cells of the host. Sixth, they may lower the "resistance" of host tissues by nullifying the actions of immune substances in the mucosa (IgA, IgG, and IgM antibodies). Seventh, no conclusive data are available from controlled studies to show that no harm results from long-term use of antimicrobial agents on a day-to-day basis for prophylactic purposes in the absence of a pathologic process. Eighth, data on delayed toxic effects from long-term use are not available. Ninth, conclusive controlled studies are not available to show that a health benefit results from long-term use of antimicrobial agents applied to the oral cavity on a day-to-day basis for prophylactic or therapeutic purposes.

The Panel has referred to the conclusions of a previous Commissioner of the FDA on the lack of evidence of effectiveness of gargles and mouthwashes containing antimicrobial ingredients from data submitted by the NAS/NRC. (See part II. paragraph B.5. above—Dosage forms of oral health care products.)

The Panel is also mindful of the position of the Council on Dental Therapeutics (Ref. 1):

> Many germicidal claims are included in mouthwash advertising directed either to the dentists or to the public. Attention should therefore be directed to the following considerations: (1) No method is yet available to give a thoroughly satisfactory comparison of germicidal agents in a test tube with the same agents under the actual conditions of their use in the oral cavity. (2) There is no adequate evidence that the average person benefits by a nonspecific change in the oral flora. (3) Some uncertainty still exists concerning the role of microorganisms as etiologic agents of many oral diseases.

OTC oral health care products are the only products containing antimicrobial agents that are used for protracted periods of time on a day-to-day basis, perhaps even spanning a lifetime. They are used for medicinal purposes when no symptoms exist or when no obvious signs of a disease are present and without any direct advice or sanction by a physician or a dentist. The Panel, therefore, concludes that antimicrobial agents should be used for oral health care only when specific symptoms, (e.g., sore throat or sore mouth) are present justifying the need for a specific product whose effectiveness has been established.

Reference

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 38th Ed., American Dental Association, Chicago, p. 343, 1979.

3. *Mode of action.* The following discussion is based on a review of several sources (Refs. 1 through 6).

Antiseptics and disinfectants exert their antimicrobial activity in a variety of ways. They may act by coagulation or denaturation of protoplasmic proteins. The phenols and certain metallic agents, such as derivatives of mercury, zinc, and aluminum, and alcohols act in this manner. Some cause cell lysis (alteration of cell membranes that causes leakage of protoplasm). They may be "surface-acting" substances which decrease the permeability of a cell by lowering surface tension at the cell membrane and fluid interface. The quaternary nitrogenous compounds or the "quats" act in this manner. (Since "the quats" are widely used in OTC oral health care products, their mechanisms of action are described in more detail below. (See part IV. paragraph A.8. below—Quaternary nitrogenous cationic antimicrobial agents.) Others act by the denaturation and inactivation of enzymes, which interferes with the metabolic activity of the cell. Some apparently penetrate into the interior of the cell by virtue of their lipid solubility and alter the intracellular biochemical activities in the membrane and within the cell. Some are oxidizing agents that act on the cell membrane or penetrate into the cells and alter the chemical structures of cellular constituents or metabolic activities of the cell.

Penetration of antimicrobial agents into the cell usually occurs by simple diffusion. It can be facilitated by substances in the extracellular fluid that decrease their solubility in the surrounding medium. Some antimicrobial agents may accumulate on the cell surface by adsorption and surround the microorganism with a dense layer of the agent resulting in altered cell permeability which makes the cell unable to function. Mercuric chloride may act in this manner. Certain antiseptics, such as phenol, that enter the cell by simple diffusion do not necessarily accumulate in its interior. They continue to penetrate into the cell and alter its structure and physiological activity. The concentration in the cell is no greater than the concentration in the solution surrounding it, but it continues to act as it moves inward. This attribute limits the safety of phenolic compounds because they act in the same manner on tissue cells of the host.

Most chemical agents that are used for topical antisepsis do not act selectively and do not exert their adverse effects solely on the microorganism. They generally injure both the cells of the host and the microorganism. The harm that results to healthy tissue cells occasionally offsets any beneficial effects that might be obtained by the action of an antiseptic.

The effectiveness of antiseptics depends upon the concentration in the medium in which it is dissolved, duration of contact with the microorganism, pH of the surrounding medium, the environmental temperature, and the presence of inorganic or organic matter. The latter may nullify the activity of many of the effective antimicrobial ingredients.

Different species of microorganisms vary in their resistance and susceptibility to an antimicrobial agent. Different cultures of the same microorganism and even different individual microorganisms in the same culture may exhibit marked variations in susceptibility to a particular antimicrobial agent.

The efficiency of any disinfectant depends on the concentration that comes into contact with the microorganism and its duration of contact. Thus, a solution of mercuric chloride whose concentration is 1:3,000 is more efficient that one whose concentration is 1:10,000. Exposure to the more concentrated solution for 2 minutes kills more microorganisms than exposure to the more dilute solution for 5 minutes. However, germicidal activity is not necessarily directly proportional to concentration. For example, concentrations of alcohol above 95 percent kill bacteria less rapidly than the 70 percent to 95 percent concentration range. Another factor that influences efficiency is the temperature

of an antiseptic to which the microorganisms are exposed. It is known that when a portion of a culture of microorganisms is added to an antiseptic solution which is maintained at a room temperature of about 20 to 25° C, far fewer organisms are killed than if the mixture were kept at 30° C, or more importantly, at a physiological body temperature of 37° C.

The effect that a solution of an antiseptic exerts usually varies inversely with the number of microorganisms present, because each microorganism withdraws a certain amount of the antiseptic from the solution and thus reduces its overall concentration. The presence of proteins has the same influence as the microorganisms in reducing the overall concentration of the antimicrobial agent in the solution. The proteins offer the antiseptics the same surface area for adsorption or combine with some of the antimicrobial agents in the same manner as do the proteins of the microorganisms. Thus, a concentration of an antimicrobial agent which is sufficient to sterilize water infected with bacteria may have little or no effect if applied to a suppurating (pus-producing) wound. The greater part of the antimicrobial agent combines with the protein in the wound; the amount that remains in the solution may be too dilute to act on the microorganisms. Therefore, many substances which are effective antimicrobial agents in aqueous or other types of solutions lose their antimicrobial activity in protein solutions. This phenomenon was one commonly referred to as the "protective action of colloids," and is due to the formation of combinations of the antiseptic with the proteins, which usually results in precipitates. These products are not dangerous to the host but they are comparatively innocuous and exert no effect on the microorganisms in the tissues. The inhibiting action of proteins may also be due partly to the fact that they limit the diffusion of an antimicrobial agent into a cell. In fact, many antimicrobial agent act on proteins generally, and are not specifically toxic fo a given type of microorganism. The lipids, like the proteins, may also lower the potency of an antimicrobial agents by combining with the agent and reducing its effective concentration.

If an antimicrobial agent is to penetrate into the interior of an organism in an effective quantity, it must be as soluble in the protoplasm as it is in the fluid in which it is incorporated. The antimicrobial agent will not leave a medium in which it is readily soluble for one in which it is less soluble. Members of the aromatic series of antimicrobial agents are very soluble in fats and oils; however, fats and oils are not suitable media for application to the infected tissues because the drug remains in the oily menstruum and fails to penetrate into the microorganism.

Mercuric chloride dissolved in alcohol has little germicidal activity. This is due to the fact that mercuric chloride, as well as salts of other heavy metals, is not dissociated (ionized) in alcohol (95 percent). The antimicrobial activity is due to the ions of metal and not to the un-ionized molecules. In order for a salt to be active it must be dissociated (ionized), and this process requires the presence of water. If the mercuric chloride is dissolved in dilute alcohol (25 percent) its effectiveness is increased because much of it is ionized, facilitating penetration of the components of the salt into the cell. The addition of inorganic salts to an aqueous solution of phenol often increases its antimicrobial activity because the solubility of the drug in water is decreased and there is a greater tendency for it to pass from the water into the interior of the microorganism.

There is some evidence to indicate that solutions containing several antimicrobial agents are more strongly antiseptic than those containing single-entity ingredients. For example, a mixture of phenol and mercuric chloride, each at less than its minimum effective concentration, is more effective as an antimicrobial agent than more concentrated solutions of either alone. This is not a hard-and-fast rule, however, and a combination may have the opposite effect. Therefore, combinations, and the concentrations of ingredients in them, must be considered individually. It is the consensus of the Panel that these drugs are all protoplasmic poisons and may harm both the cells of the host as well as the pathogenic organism. For the sake of safety, preparations containing single-entity active ingredients are preferred.

Some OTC products contain less than the minimum inhibitory concentration of a chemical. Such solutions merely retard the growth of microorganisms. Concentrations of substances that are too dilute to kill microorganisms are bacteriostatic and may merely act as preservatives. Antiseptic claims cannot be made for them and to do so is both misleading and a misbranding of a product.

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 803–804, 1957.

(2) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 884, 1977.

(3) Grollman, A., and D. Slaughter, "A Textbook of Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 771–775; 1947.

(4) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 987–1009, 1975.

(5) Block, S. S., "Disinfection, Sterilization, and Preservation," Lea and Febiger, Philadelphia, 1977.

(6) Hugo, W. B., "Inhibition and Destruction of the Microbial Cell," Academic Press, London, 1971

4. *The microbiology of the oral cavity*—a. *Changes of the oral flora with age.* The oral flora changes from birth through the primary, mixed, and permanent dentitions. There are also differences in the oral flora following extraction of all the teeth and their replacement with dentures. The oral cavity normally supports a concentrated and varied microbial population, the heaviest concentrations being on the dorsum of the tongue, around the gingival sulcus, and on the surfaces of the teeth.

At birth, the oral cavity is usually sterile despite inoculation with the indigenous flora of the mother's genital tract, which is comprised of lactobacilli, corynebacteria, micrococci, coliforms, aerobic and anaerobic streptococci, yeasts, protozoa, and sometimes viruses. The first 8 hours following birth show a rapid increase in the number of detectable organisms. For the first few days of life, the bacterial composition varies considerably. The organisms have been reported to include several species of lactobacilli, streptococci, staphylococci, pneumococci, enterococci, veillonellae, anaerobic streptococci, coliforms, sarcina, and neisseriae. With the exception of *Streptococcus salivarius,* most of these organisms are found sporadically but not in high numbers. The newborn's mouth is highly selective even within the first few days. Practically none of the bacteria common to the general environment become established, and only a few of the microorganisms inhabiting adult mouths occur persistently at this time.

By the end of the third month, all mouths support a microbiota beginning to resemble that of the adult. At the end of the first year of life, however, only streptococci, staphylococci, veillonellae, and neisseriae are generally found in all

mouths. Actinomyces, nocardiae, lactobacilli, and fusobacteria can be cultured from about one-half of the mouths. Bacteroides, leptotrichiae, corynebacteria, and coliforms are isolated from less than half of the mouths. Streptococci still predominate numerically. Infancy is dominated by facultative species, to which are gradually added the various obligate anaerobes, but numerically the facultative types generally dominate at all ages (Refs. 1 and 2).

In preschool children, the proportions of predominant cultivable organisms from the gingival crevice area resemble those in adults, except that *Bacteroides melaninogenicus* and spirochetes are not present in all children. *Bacteroides melaninogenicus* is present in virtually all adolescents. Spirochetes also increase in incidence with age. The presence of dental caries (cavities) also influences the oral flora by providing new ecological niches for multiplication, new substrates, and a more acidic pH.

Tables 1 and 2 shows the predominant genera and species found in various sites (Ref. 2).

With the loss of teeth, spirochetes, lactobacilli, and some strains of streptococci are reduced. Shklair and Mazzarella's (Ref. 3) studies demonstrated that lactobacilli and yeasts virtually disappear during the edentulous period and that *Streptococcus salivarius* increases. During the first 2 weeks after placement of the dentures, streptococci remain at a high level while lactobacilli and yeasts gradually return, but remain at a low level. After 3 to 5 weeks the lactobacilli and yeasts increase, and the streptococci decrease to preextraction levels. During the entire period, the number of staphylococci do not fluctuate significantly.

TABLE 1.—MEAN PERCENTAGES OF CULTIVABLE ORGANISMS IN THE ADULT ORAL CAVITY (Ref. 2)

Organism	Saliva	Percentage		Tongue
		Gingival crevice area	Dental plaque	
Gram-Positive Facultative:				
Cocci	46.2	28.2	28.2	44.8
Streptococci	41.0	27.1	27.9	38.3
Streptococcus salivarius	4.6	N.D.	N.D.	8.2
Enterococci	1.3	N.D.	N.D.	7.2
Staphylococci	4.0	1.7	0.3	6.5
Gram-Positive Anaerobic:				
Cocci	13.0	7.4	12.6	4.2
Gram-Negative Facultative:				
Cocci	1.2	0.4	0.4	3.4
Gram-Negative Anaerobic:				
Cocci	15.9	10.7	6.4	16.0
Gram-Positive Facultative:				
Rods	11.8	15.3	23.8	13.0
Gram-Positive Anaerobic:				
Rods	4.8	20.2	18.4	8.2
Gram-Negative Facultative:				
Rods	2.3	1.2	N.D.	3.2
Gram-Negative Anaerobic:				
Rods	4.8	16.1	10.4	8.2
Fusobacterium	0.3	1.9	4.1	0.7
Bacteroides melaninogenicus	N.D.	4.7	N.D.	0.2
Vibrio sputorum	2.1	3.8	1.3	2.2
Other Bacteroides	2.4	5.6	4.8	5.1
Spirochetes	N.D.	1.0	N.D.	N.D.

N.D.=not detected.

TABLE 2.—PERCENT DISTRIBUTION OF ORGANISMS IN DIFFERENT SITES IN THE HUMAN ORAL CAVITY (REF. 2)

Organism	Supragingival plaque	Tongue	Gingival crevice	Cheek	Saliva
S. mutans	3.9	0.3	.....	0.5	0.2
*S. sanguis**	75.0	9.0	.....	29.0	47.0
*S. salivarius**	0.7	55.3	0.5	10.7	47.4
*B. melaninogenicus***	0.3	0.4	4.5	0.3	0.42
Spirochetes***	0.1	.....	1.5	.....	.....
Lactobacillus	0.0001	.....	.....	.....	0.01

*Percent of facultative streptococci.
**Percent of total cultivable flora.
***Percent of microscopic count.

b. *Problems associated with the study of the oral microbial flora.* It is difficult to obtain definitive information concerning the location, kinds, and numbers of oral microorganisms because of problems of variability, sampling, cultivation, enumeration, and identification. Even in a single mouth the microbial population undergoes progressive changes until maturity, and there are wide fluctuations thereafter.

Diet plays an important role in the growth of microoganisms as do the host tissues and other microoganisms. The nature and amount of proteins and carbohydrates will determine which organisms will flourish and which will remain static. The amount of sucrose in the diet can influence the amount of plaque, the population density, and the percentage of *Streptococcus mutans* and *Streptococcus sanguis* in the plaque.

Essential metabolites for some bacteria are produced by other bacteria. For example, formic and lactic acids produced by bacteria in the oral cavity in part supply the energy sources for *Veillonella alcalescens.*

The bacteria from the human oral cavity have a wide variety of oxygen tension requirements. Obligate aerobes facultative aerobes, microaerophiles, anaerobes which tolerate oxygen exposure but multiply only in its absence, and strict anearobes which will not survive even momentary exposure to oxygen, have all been identified.

c. *The organisms comprising the oral microbiota.* The number of so-called species of bacteria indigenous to the oral cavity are innumerable since their

recovery depends greatly upon the methodology used for their cultivation. The variations from person to person and from site to site are great. The recent use of anaerobic transport solutions for the specimen and the anaerobic chamber for all manipulations during cultivation have increased enormously the number of genera and species which are associated with various areas of the mouth, especially that of the gingival crevice and periodontal pocket.

Mycoplasma species can be demonstrated in all adult mouths. They have been isolated from saliva, plaque, and calculus; they have also been isolated from samples obtained from healthy and diseased gingival crevices and various lesions. Protozoa can be demonstrated in small numbers in approximately 50 percent of clean and healthy mouths. A much higher incidence is associated with poor oral health care and periodontitis (Ref. 1).

References

(1) Burnett, G. W., and G. S. Schuster, "Oral Microbiology and Infectious Disease," Williams and Wilkens, Baltimore, pp. 141–173, 1978.

(2) Socransky, S. S., and S. D. Manganiello, "The Oral Microbiota of Man from Birth to Senility," *Journal of Periodontology,* 42:485–496, 1971.

(3) Shklair, I. L., and M. A. Mazzarella, "Salivary Microbial Changes as a Result of Full Mouth Extraction," Dental Research Facility, U.S. Naval Training Center, Great Lakes, IL, Project MR005. 12–5004, (NM 75 01 27), 1960.

5. *The mircobial flora of the pharynx and upper respiratory tract.* The bacterial flora of the oral cavity and that of the pharynx and upper airways are, in most respects, not remarkably different, since there is an intermingling of the secretions of the mouth and throat. However, there is a gradual transition in composition along the pathway from the lips, gums, mouth, and throat into the trachea and bronchi. As is the case in the oral cavity, the ecology, i.e., the relationships between organisms and interrelationships between the organisms and their environment, is important (Refs. 1 through 6). In the mouth, numerous microbial species reside in the oral and hypopharynx and the upper respiratory tract of man under normal conditions. Some are regularly demonstrable as major permanent residents. These include many species of streptococci, both faculative and anaerobic, with the alpha hemolythic "viridans group" predominant, leptothrichia, several species of corynebacteria ("diphtheroids"), a variety of neisseria species (e.g. *Neisseria catarrhalis, Neisseria pharyngitidis*). as well as the potentially pathogenic *Staphylococcus aureus.* Anaerobes includes the veillonella, vibrios, spirochetes, fusobacteria, bacteroides, and many others too numerous to list here. In addition, coliform bacteria, proteus, pseudomonas, and others which are predominant residents of the normal intestinal flora may occasionally reside in the mouth and throat in small numbers. Pathogenic microorganisms may exist within the indigenous oral flora of persons who have recovered from some infectious disease process. These have established an equilibrium with the other organisms ordinarily present and exist without causing a pathologic process. Persons harboring such microorganisms may, of course, be carriers and may be a source of infection for other persons with whom they have contact (Ref. 4).

Knowledge of the composition of the indigenous microbial flora of the naso-, oro-, and laryngopharynx is just as important as knowledge of the composition of the indigenous microbial flora of the oral cavity. For instance, in evaluating laboratory reports concerning bacteriological examination of clinical specimens, the physician must often judge whether the isolated organisms are indigenous flora and can be disregarded, or are pathogenic and may cause symptoms in an individual patient. Marked differences in the composition of the indigenous microbial flora may be observed among different individuals. These differences depend upon numerous variable factors, such as pH and viscosity and composition of the saliva. Various degrees of compatibility exist among groups of bacteria, based on differences in metabolic activities and growth requirements. In addition, variable factors in the host may be equally as important, if not more important, in creating a specific ecological composition and equilibrium of the bacterial flora. Living habits, food preferences, hormonal or metabolic peculiarities, and other factors probably exert specific influences in determining the nature of the microbial flora of the naso-, oro-, and hypropharynx (Ref. 4).

The existence of an ecological balance between various types of microorganisms supports the concept that the indigenous flora serves as a strong and an effective natural barrier against invading pathogens. In many instances, the invader encounters an environment which is unfavorable to its gaining a foothold and surviving within the biosystem of the existing flora. Any disturbance of the indigenous flora, however, can create an environemnt which could give invading pathogens an opportunity to gain a foothold and establish residence in the upper air passages. Even an imbalance among microorganisms ordinarily present in the indigenous flora can lead to multiplication of their numbers and a pathological state, since some microorganisms that are normally present may be opportunistic pathogens. It is for this reason that the use of antimicrobial agents in the absence of symptoms of a pathologic state is considered irrational and possible harmful (Ref. 4).

Disturbances of the normal flora of the throat may occur from many causes. Some are due to local factors, some to general factors, and some to a combination of both general and local factors. Chemical or physical irritation, local allergic reactions, and anatomical abnormalities, such as mucosal atrophy or functional changes, may have a direct local effect on the bacterial flora. Causative factors of a systemic nature include nutritional deficiencies, avitaminosis, unbalanced metabolic disorders (diabetes), and other similar pathological states. However, the most frequent and also in most cases a dangerous cause is the unwarranted use of antimicrobial agents. All types of antimicrobial agents can be incriminated but most noteworthy are the antibiotics. For whatever reason and in whatever form antibiotics are administered to a patient, they may alter the normal bacterial flora because the drug-susceptible microorganisms will be killed or their metabolic activity inhibited. Often no overt consequence follows the use of an antibiotic and the flora shifts back to its previous composition and equilibrium when use of the drug is discontinued. In some cases, and organism develops mechanisms that overcome adverse effects of the antibiotic and continues to proliferate in its presence. This phenomenon, called drug resistance, occurs frequently. The danger of a disease process resulting from an alteration of the compositon of the indigenous bacterial flora must not be underestimated; moreover, the possibility of the occurrence of this response is of equal importance as the development of drug resistance (Ref. 4).

a. *Disease-producing properties of microorganisms.* Some organisms, especially fungi, cause disease simply by their presence in the tissue. The tissue responds by developing a foreign body reaction with the subsequent formation of granulomas. As the microorganisms multiply and consume nutrients, inadequate nourishment of the tissue may lead to irreversible damage

or even necrosis. Fungal infections are more apt to cause sore mouth than sore throat.

Many gram-negative microorganisms contain endotoxins. These are complex molecules consisting of a protein combined with a liposaccharide. When released in the tissues of a host they cause toxic manifestations. The endotoxins are usually present in the cell wall of the microorganism. They are released upon death and disintegration of the microbial cells and pass into the tissue fluids or blood. Free endotoxin causes local edema, hemorrhage, and possibly necrosis. Bloodborne endotoxins cause systemic generalized symptoms that include, fever, nausea, vomiting, diarrhea, oliguria, hematuria, and even anuria. Shock of various degrees, dependent on the amount and virulence of the endotoxin liberated into the circulation, is a common manifestation.

Other microorganisms produce exotoxins which are excreted locally into their environment where they are absorbed, become bloodborne, and act systemically. Most exotoxin producers are of the gram-positive type, including *Staphylococcus aureus,* which is often indigenous in the mouth, and *Strepotococcus pyogenes.* Minute amounts of an exotoxzin are sufficient to cause severe damage to specific organ or cell systems. These organs or cell systems may be distant from the focus of infection.

Some microorganisms release enzymes, which increase their invasiveness. A great variety of important pathogenic enzymes elaborated by microorganims have been described. The organisms involved in their production include *Strepotococcus pyogenes* and *Stapohylococcus aureus.* The enzymes elaborated include hyaluronidase, proteinases, fibrinolysins, collagenases, and numerous others, most of which may facilitate spread of infection in the tissue (Ref. 4).

(1) *Streptococci.* Streptococci are found in the throats of both human beings and animals. *Streptococcus pyogenes* may cause severe sore throat and generalized systemic manifestations, such as fever, joint pains, etc. They are grounded on the basis of antigenic properties, and these groups possess varying degrees of host specificity. Group A streptococci (*Streptococcus pyogenes*) cause 90 percent of the streptococcal infections in human beings. The natural reservoir of human pathogenic streptococci is the respiratory tract of persons who have developed an immunologic equilibrium with these bacteria and are asymptomatic carriers. Other groups of pathogenic streptococci are found under similar conditions in various animal species. Nonpathogenic streptococci are abundant among the indigenous flora of the upper respiratory tract and mouth. They inlcude the "viridans groups" of streptococci found in the mouth and throat, enterococci (including group D-streptococci) found in the mouth and oropharynx, as well as anaerobic streptococci (e.g. peptostreptococcus) found in the respiratory tract and mouth. Any of these strains can, under certain conditions, become pathogenic. Such pathogenicity may be expressed when the equilibrium of the indigenous oral flora is disturbed or when the organisms are introduced into other areas of the body which they do not normally inhabit. Typical examples of disease processes they may cause are dental pulpitis, periodontal abscesses and subacute bacterial endocarditis (usually due to the "viridans group" of streptococci).

About half the human population develops a delayed type of hypersensitivity against streptococcal substances. This can be demonstrated by skin testing with streptococcal extract (Refs. 1 through 4).

(2) *Pneumococci.* Pneumococci are closely related to streptococci and, if pathogenic, most often cause bacterial penumonia. Certain antigenic types are particularly apt to produce disease; others are seldom pathogenic and are part of the indigenous flora of the upper respiratory tract. They may become pathogenic if the bacterial flora is altered and an imbalance occurs. Such an alteration may occur from the unwarranted use of antimicorbial agents.

(3) *Staphylococci.* The important pathogenic member in this group is *Staphylococcus aureus* which causes purulent infections in animals and human beings alike. It is ubiquitously present on the skin and in the nose and throat. Usually a well-balanced equilibrium exists between the host and this type of microorganism. This equilibrum may be disturbed by mechanical irritation, allergic reactions of the mucous membranes, traumatic lesions, nutritional deficiencies or hormonal imbalances, such as occurs in diabetes, thyroid disease, and so forth. Patients may acquire antimicrobial-resistant staphylococci and incorporate them into their normal bacterial flora, especially in hospital environments. If a resident strain of *Staphylococcus aureus* is antimicrobial-resistant, application of the particular antimicrobial agent would give the organism a growth advantage by killing or inhibiting the growth of organisms that are antagonistic to the staphylococcus (Ref. 4).

(4) *Neisseria.* Several species of non-pathogenic neisseria are part of the indigenous flora in the pharynx and upper respiratory tract. Among these are *Neisseria catarrhalis* and *Neisseria pharyngitidis.* The pathogenic members of this genus, *Neisseria meningitidis* and *Neisseria gonorrhoeae,* cause disease exclusively in human beings. *Neisseria meningitidis* inhabits the throat of about 5 percent of normal persons but shows little tendency to spread to noncarriers. Restricted outbreaks of meningococcal meningitis occur in special epidemiological situations, usually among people who live in crowded conditions. The species of *Neisseria meningitidis* can be subdivided into three serological types: A, B, and C. Type B is now encountered most often in epidemics, whereas 1 or 2 decades ago type A was more prominent. Type C is occasionally found in sporadic infections (Ref. 4).

(5) *Corynebacteria.* Nonpathogenic corynebacteria (diphtheroids) constitute a large portion of the indigenous flora of the mucous membranes of the throat.

(6) *Haemophilus influenzae. Haemophilus influenzae* is frequently found in the respiratory tract of normal persons. If the organism lacks a capsule, it is usually avirulent. Primary infections due to capsulated strains occur, especially in children. Severe forms of the disease may also cause meningitis. *Haemophilus influenzae,* as in the case with streptococci, pneumococci, or staphylococci, may play a role in secondary bacterial infections of viral diseases such as influenza-pneumonia. In fact, it was considered by its discoverer to be the etiological agent of influenza.

(7) *Mycobacteria.* The two diseases caused by mycobacteria are tuberculosis and leprosy. Both may cause infections in the throat and larynx, although these are rare. The manifestations are usually part of a chronic pulmonary or other systemic infection (Ref. 4).

(8) *Spirochetes.* Three genera of human pathogenic spirochetes are recognized: borrelia, treponema, and leptospira. Only the first two are of special interest in oral diseases. Both genera contain species which are components of the indigenous flora. They may become opportunistic pathogens, as is the case with *Borrelia vincenti,* which is associated with Vincent's angina, cancrum oris, and gangrenous processes in the throat and other parts of the upper respiratory tract. *Treponema pallidum,* the

causative agent of syphilis, is of interest since in the secondary phase of the disease it is particularly apt to cause pharyngitis.

The Panel emphasizes that infections caused by the aforementioned bacteria are not "minor," may be serious and require the expertise of a dentist or physician, as well as a microbiologist for their recognition. The conditions they cause are not amenable to self-diagnosis and unsupervised self-treatment with antimicrobial and other health care products.

b. *Viruses causing disease of the oropharynx.* The number of respiratory tract diseases caused by viruses is indeed great. Over 250 viruses are believed to cause the common cold. Current treatment of viral infections involves active and passive immunoprophylaxis. None of the agents used for this purpose are available OTC. OTC antimicrobial agents are of no therapeutic benefit (Ref. 5).

Viruses causing disease of the throat include the coxsackie A virus, herpes virus, infectious mononucleosis virus, and mumps virus. Other viruses which primarily cause acute pharyngitis are discussed below.

(1) *Coxsackie A virus.* Several serological types of coxsackie A viruses have been associated with lesions of the mouth and oropharynx. There are at least 23 immunologically distinct coxsackie A types. The coxsackie A viruses have been shown to cause not only respiratory tract disease but also aseptic meningitis, paralysis, exanthemas, and hepatitis (Ref. 5).

Herpangina is a clinical syndrome which occurs mostly in the summer and mainly affects children. The illness is featured by an acute onset of fever, sore throat, and dysphagia. It is sometimes accompanied by abdominal pain, myalgia, headache, and vomiting. The characteristic feature of the syndrome is the presence of small, scattered vesicles in the oropharynx, each surrounded by an erythematous zone. They are located on the anterior pillars of the fauces, but can also occur on the palate, uvula, tonsils, and tongue. They do not usually occur on the gingival or buccal mucosa. The individual lesion appears first as a grayish white papule or vesicle about 1 to 2 mm in diameter which is surrounded by a red areola. After several days the areola becomes more intensely red, the vesicles enlarge and become shallow grayish ulcers. Both vesicles and ulcers may be present at the same time. Usually there are 4 to 5 lesions, but as many as 14 or 15 have been seen. The course of the illness is usually benign. There have been reports of parotitis complicating herpangina.

Coxsackie A–10 has been associated with an epidemic of acute lymphonodular pharyngitis in children. The patients had fever, headache, and sore throat from 4 to 14 days. The distinct lesions were discrete whitish or yellowish nodular papules on the uvula, anterior pillars, and posterior pharynx which did not vesicate. Histological examination of the nodules revealed the papules to be formed of tightly packed lymphocytes. There is no specific treatment for coxsackie A disease (Ref. 5).

(2) *Infectious mononucleosis.* Infectious mononucleosis (IM) is an acute infectious disease of presumed viral etiology, which causes sore throat, that occurs predominantly in children and young adults. The search for the etiology of IM is closely associated with the Epstein-Barr (EB) virus. The EB virus is a member of the herpes group and was first detected in cultures of Burkitt's lymphoma cells. The association of the virus with IM is based on a serological relationship. Individuals with IM develop antibody to EB virus in their serum (Ref. 5).

(3) *Viral upper respiratory diseases.* Although exact data are difficult to obtain, it is generally agreed by most authorities that acute upper respiratory tract infections (URI or the common cold) are the greatest cause of morbidity in the United States (Ref. 5).

Viral respiratory illnesses are caused by numerous groups of viruses. The viruses produce a variety of clinical syndromes. Any individual virus group is capable of causing a multiplicity of syndromes, and a particular syndrome can be caused by various groups of viruses.

There appears to be a difference in the morbidity caused by these viruses in children and in adults. This is probably the result of the acquired immunity, which is present in adults and not in children.

The verification that the disease is of viral etiology is wholly dependent upon laboratory tests (Ref. 5).

(4) *Adenoviruses.* The adenoviruses were first isolated in 1953 by culturing adenoid tissue from children undergoing adenoidectomy. At least 31 immunologically distinct adenoviruses have been identified, 9 of which have been associated with respiratory tract infections. Synonyms are adenoid degeneration (AD) agents, acute respiratory disease (ARD) viruses, and adenoidal-pharyngeal-conjunctival (APC) viruses.

The clinical syndromes associated with adenovirus infections include undifferentiated acute respiratory disease, pharyngoconjunctival fever, and pneumonia. Clincial signs of undifferentiated acute respiratory disease include sore throat (pharyngitis), cervical lymphadenopathy, cough, chills, fever, malaise, and headache. Coryza and fever may be present. The clinical signs of pharyngoconjunctival fever include fever, pharyngitis, conjunctivitis, and frequently gastrointestinal pain. Pneumonia or severe respiratory tract involvement occasionally occurs (Ref. 5).

(5) *Influenza viruses.* Influenza viruses, which are members of the myxovirus family have had a profound effect on people. Pandemics of influenza have taken severe tolls in morbidity and mortality throughout history. These pandemics have been due to alteration in the antigenic makeup of influenza viruses approximately every 10 years for the past 30 years.

The influenza viruses are divided into three types, A, B, and C, on the basis of their neucleocapsid and M protein antigens. Each type is further divided into antigenic subtypes, which differ from each other by the composition of their surface glycoproteins (hemagglutinin and neuraminidase). A continuous genetic shifting of the antigenic configuration of the viruses creates "new" viruses for which the population has no antibodies and, therefore, immunity most likely has resulted in pandemics of influenza (Ref. 1, 2, 3, 5, and 7).

Influenza viruses can cause a wide spectrum of respiratory tract disease, ranging from subclinical infection to fulminating pneumonia. However, the typical case of influenza is a systemic disease which is familiar to all physicians. After a short incubation period of one to three days, coryza, cough, sore throat, headache, fever, malaise, anorexia, and frequently nausea and vomiting occur accompanied by an apathetic appearance. The illness persists for a week to 120 days and is usually followed by a prolonged period of convalescence in which the patient is somewhat lethargic or "not up to par." Pneumonia, either of purely viral origin or caused by a secondary bacterial invader, or of a mixed infection of viral and bacterial etiology, is the most common complication. Other complications are meningoencephalitis and myocarditis, but these are quite rare (Ref. 5).

(6) *Para-influenza viruses.* The para-influenza viruses were first isolated during the 1950's. Four distinct serologic types have been recovered in the throat of human beings (Ref. 5).

(7) *Rhinoviruses.* The rhinoviruses are the most recently isolated viruses to be

referred to as "the common cold virus." The initial rhinovirus isolates were made in 1954 from afebrile individuals with coryza, sore throat, and cough. There are probably over 100 distinct serological strains of rhinoviruses. Currently some 60 specific serological types have been classified. No antimicrobial agents are available that exert any therapeutic effect on these viruses. The common cold is actually a misnomer since so many different viruses can afflict people and cause similar symptoms, coryza, sore throat, and systemic manifestations such as malaise, fever, etc. The term might be considered a proper one to use if the symptom complex were caused by a single virus (Ref. 5).

(8) *Coronaviruses.* The coronaviruses are a relatively newly described group of viruses which are also associated with the common cold. The name is derived from the fact that, when visualized with the electron micrograph, the human coronavirus resembles a crown (Ref. 5).

c. *Fungal infections.* Fungal infections, also known as mycoses, have been playing an increasingly important role in conditions affecting the mouth, nose, and throat for several reasons: (1) There is greater awareness of their presence; (2) better diagnostic facilities are available; (3) the incidence is increased because of therapeutic interference (antibiotics, immunosuppressive drugs, radiation); and (4) there is increased longevity in such diseases as lymphomas, other neoplasms, and hematologic disorders (Ref. 6).

Conditions favorable to the development of mycoses prevail in the mouth and throat, where a moist, warm environment, and such crevices as tonsillar crypts and periodontal spaces encourage growth. They are also found in the nasopharynx and nose where such conditions as obstructive lesions and deviated nasal septa favor the growth of fungi and related organisms. Actinomyces and nocardia are now universally accepted as bacteria, but are traditionally discussed with fungi because of the close resemblance between the symptomatology and course of the diseases they cause. A discussion of the oral and pharyngeal lesions most commonly due to fungal infections can be found earlier in this document. (See part II. paragraph B.4.b. above—Sore mouth.)

The diagnosis of mycosis depends upon the availability of a well-equipped laboratory and the use of modern immunologic and staining procedures. Contrary to widespread belief, biopsies and not cultures are the most rapid and commonly successful tools for diagnosis of fungal disease. Biopsy material should be divided into two specimens, one for cultural studies and one for staining. The selection of proper media by the laboratory is necessary since some organisms require special cultural conditions (Ref. 6).

Candidiasis, the fungal disease which occurs in the mouth most commonly, is caused by the yeast-like organism *Candida albicans.* It covers a wide range of manifestations. (See part II. paragraph B.4.b. above—Sore Mouth.) Candidiasis is most often found about the oropharynx. The small yeast (2 to 5 um) is ovoid, appears intensely blue with the Gram stain, and can be demonstrated with any of the numerous stains for fungi. Broad hyphae can be seen in association with the yeast cells. Often it is quite obvious that the hyphae are just elongated yeast cells when budding takes place at the point of constriction. The incidence of *Candida albicans* in the mouth and throat varies from country to country and depends on age, hygiene, presence of other diseases, use of broad-spectrum antibiotic therapy, and so forth (Ref. 6).

A mild form of candidiasis is thrush, a white to grayish membranous formation over tonsils or adjacent mucosae, which occurs either in discrete or confluent specks and which can often be removed with a swab. Smears of such membranes rule out diseases such as diphtheria, the ulcerations of infectious mononucleosis, or acute leukemia. Thrush is seen most often at the extremes of age, in the (often premature) newborn who acquire the disease in the maternal birth canal, and in the geriatric patient, dying of old age or from tumors. Thrush, therefore, is often a warning signal of some profound abnormality existing in the body and does not itself require energetic therapeutic measures (Ref. 6).

References

(1) Gwaltney, J. M. "Pharyngitis," *in* "Principles and Practice of Infectious Disease," edited by G. L. Mandell, R. G. Douglas, and J. E. Bennett, John Wiley and Sons, New York, pp. 435–441, 1979.

(2) Gwaltney, J. M., "Acute Laryngitis," *in* "Principles and Practice of Infectious Disease," edited by G. L. Mandell, R. G. Douglas, and J. E. Bennett, John Wiley and Sons, New York, pp. 441–442, 1979.

(3) Hall, C. B., "Acute Laryngotracheobronchitis, Croup," *in* "Principles and Practice of Infectious Disease," edited by G. L. Mandell, R. G. Douglas, and J. E. Bennett, John Wiley and Sons, New York, pp. 442–449, 1979.

(4) Brand, K. G., "Bacteriology: Basic and Applied to Otorhinolaryngology," *in* "Otolaryngology: Volume 1. Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 411–427, 1973.

(5) Schiff, G., "Viral Disease in Otolaryngology," *in* "Otolaryngology: Volume 1. Basic Sciences and Related Disciplines." edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 428–422, 1973.

(6) Schwarz, J., "Mycoses," *in* "Otolaryngology: Volume 1. Basic Sciences and Related Disciplines," edited by M. M. Paparella and D. A. Shumrick, W. B. Saunders Co., Philadelphia, pp. 443–453, 1973.

(7) Davis, B. D., et al., "Microbiology," 2d Ed., Harper and Row, Hagerstown, MD, pp. 1314–1315, 1973.

6. *Evaluation of antimicrobial activity.* One of the requests made of the Panel was to recommend testing procedures whereby a Category III product could be reclassified to Category I. The Panel has made such recommendations and suggestions concerning testing for antimicrobial ingredients for oral health care products. (See part IV. paragraph C. below—Data Required for Evaluation.) The Panel has suggested a general in vitro test that may be used as a guide, but which may be modified to suit individual protocols for testing a specific ingredient for specific purposes.

It is the concensus of the Panel that it is not possible to suggest an in vivo method of a general type that would encompass all criteria necessary to evaluate the effectiveness of all antimicrobial agents claimed to be effective in relieving symptoms of sore throat and sore mouth due to antimicrobial activity. The Panel had considered an in vivo method based on plaque reduction on the teeth and periodontal tissues as a criterion for antimicrobial activity in the oral cavity, but discarded it because it became obvious that it was inexact and had no rational basis since dental plaque is not a disease per se (Ref. 1 through 4). Moreover, the Panel was not charged with reviewing products used to treat dental or periodontal diseases. Some clinicians and microbiologists specializing in dental microbiology have used plaque reduction as a criterion of effectiveness of antimicrobial agents in mouthwashes and have submitted data in support of their effectiveness of such products based on this concept. The rationality of plaque reduction as a criterion of effectiveness of antimicrobial agents for use in the mouth and throat is highly debatable, and evidence of the validity of the method is scant. Plaque reduction, therefore, is not accepted by this Panel as a criterion for determining effectiveness of antimicrobial agents for oral health care products intended to treat sore mouth or sore throat.

Dental plaque has been described as a soft and tenacious material found on surfaces of teeth readily removed by mechanical means such as brushing or flossing, but not readily removed by rinsing with water and other solutions (Ref. 5). The composition of plaque is multivaried, consisting of proteins, carbohydrates, clumps of microorganisms, and other organic and inorganic materials. The amount, as well as the microbial and biochemical composition of plaque, varies with the site of formation, the duration of accumulation, the composition of the diet, and perhaps other undetermined factors (Ref. 6). Both dental caries and periodontal disease are attributed to plaque. The Panel, however, was not charged to consider dental plaque and periodontal diseases. The Panel has never stated that plaque is not involved in causing dental caries and periodontal diseases.

It is noteworthy that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, in its report which was published as a proposed regulation in the **Federal Register** of November 2, 1979 [44 FR 63274], states:

To supplement mechanical removal of offending agents, a number of chemical agents claiming usefulness for prevention of plaque, calculus, or gingivitis are presently under investigation. The potential value and safety of these agents, which include quaternary ammonium compounds, enzymes, organic fluorides, and various antibiotics, have not been conclusively ascertained. The specific antimicrobial compounds for which some success is claimed in clinical studies include several agents. Among them are cetylpyridium chloride and combinations of cetylpyridium chloride and domiphen bromide which achieved a 30- to 40-percent reduction in dental plaque (Refs. 7 and 8). Other potentially effective agents include thymol and eucalyptol (Ref. 9), alexidine (Ref. 10), peroxides (Ref. 11), chlorhexidine (Ref. 12), and an investigational compound CC10232 (Ref. 7). A major concern in the use of these agents is their tendency to disrupt the normal microbial ecologic balance of the host (Ref. 13).

After considering these ingredients and the theories and rationale proposed for the effectiveness of drugs used for prevention and control of plaque and gingivitis, the [Dental] Panel has concluded that such approaches are at present so controversial that there can be no general recognition of the effectiveness of these agents for these indications at this time.

The [Dental] Panel, therefore, recommends that all claims stating or implying prevention, control, or treatment of plaque or gingivitis be placed in Category II and further recommends that antiplaque and antigingivitis agents be investigated and approved through the NDA process.

Additionally, the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products stated at 44 FR 63283 that:

The [Dental] Panel concludes that drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time. Accordingly, the Panel recommends that such drug products and claims should be evaluated by FDA through the NDA procedure.

The rationality of plaque reduction, as a criterion of effectiveness for antimicrobial agents that are used in the mouth and throat, is highly debatable and evidence of the validity of the method is scant. There was considerable discussion of this issue in the deliberations of the Panel and in making its final determination the Panel relied upon the opinions of consultants and statisticians who are experts in this field of endeavor, in addition to relying upon the expertise of the Panel. At the January 4, 1979 meeting of the Advisory Review Panel on OTC Oral Cavity Drug Products, Dr. S. S. Socransky, Dr. W. H. Bowen, and Dr. F. B. Engley were invited as consultants to present their views on plaque reduction.

In his presentation, Dr. Socransky stated:

What does the particular [antimicrobial] agent do? What is it active against? If you are cutting down microorganisms in the oral cavity, which I gather is the claim of this particular agent, then precisely what is the effect of cutting down these microorganisms in the oral cavity? Does it have some effect on microbial infection, bites, and things like that, or does it have an effect on dental caries, periodontal disease, or anything else? Or is it merely an effect on bacterial infestation just accumulations of organisms in the mouth?

I do not think from the evidence that we have seen that you can go beyond making the claim at this moment that this is cutting down the numbers of organisms in the mouth temporarily. It is not clear that this is cutting down infections of the oral cavity, such as those induced by bites or something of that type, nor is it clear to me, at any rate, that it has an effect on caries, or periodontal diseases of any type in any striking fashion.

When one cuts down the bacterial plaque, or any bacterial accumulations on tooth surfaces, I am not sure which organisms are influenced by anything that I have seen so far, and it could be possible that one is cutting down on harmful microorganisms, which is certainly reasonable.

It is equally possible that somebody is cutting down on organisms that are potentially beneficial.

So to clarify this role, I think that despite some of the concerns with some of the statistical handling of the information there is a cutdown in bacterial plaque to a degree. The amount that is reduced varies from very little to a great deal, depending on the study one reads.

The significance of this in terms of beneficial effect, which is apparently what the public is after, is unclear to me.

What has been used has been an area measurement, primarily, in the index—a weight measurement in terms of wet weight. There have been few, if any, that I have read of, actual measurements of numbers of microorganisms.

Dr. Bowen continued the presentation by stating:

The question that [Dr. Socransky] has also raised is that even if we accept that there is an antimicrobial effect which results in the production and formation of plaque by a certain percentage, I am unclear what this means to a patient or subject who uses.

Plaque is not a disease. It is probably a potential disease-producing entity. Its presence does not invariably result in disease; and, while there may be reasons for simply removing dental plaque, certainly I would think that the general public believes that if they had a small percentage in reduction of plaque, they might, in fact, have a reduction in disease. That is not necessarily so.

Dr. Engley stated that reduction of plaque is an unclear term:

When you say reduction, you are talking about size and weight, but you are not talking about the numbers of organisms in the plaque. Sometimes you can reduce the glucan or the capsular material or the envelope material and come out with the same number of organisms but lower volume and lower weight.

Statistical data relevant to antimicrobial activity were submitted to the Panel and subsequently reviewed by a consultant statistician at the request of the Panel. The following is a summary of his comments:

Data have been presented which indicate effectiveness of domiphen bromide, the combination of CPC [cetylpyridinium chloride] and domiphen bromide, and the combination of menthol, thymol, eucalyptol, and methyl salicylate. The effectiveness relates to plaque reduction as measured by the Quigley-Hein index or the Turesky modification on the Quigley-Hein index. This index measures surface area of plaque. Before an antimicrobial claim is appropriate it must be established that the reduction in the Quigley-Hein index correlates with an antimicrobial action. None of the studies mentioned above attempt to do this. The claim that appears to be appropriate given the above studies is a claim dealing with surface area of plaque within a 7- to 21-day period.

The Panel, therefore, does not regard as valid and has not accepted data on

effectiveness of antimicrobial agents in oral health care products for treating sore throat and sore mouth based upon their ability to inhibit plaque formation.

References

(1) Cohen, B., "The Essential Nature of Periodontal Disease," *in* "Scientific Foundations of Dentistry," edited by B. Cohen and I. R. H. Kramer, William Heinemann Medical Books Ltd., London, pp. 439–447, 1976.

(2) Page, R. C., and H. E. Schroeder, "Pathogenesis of Inflammatory Periodontal Disease: A Summary of Current Work" *Laboratory Investigation,* 33:235–249, 1976.

(3) Sutcliffe, P., "A Longitudinal Clinical Study of Oral Cleanliness and Dental Caries in School Children," *Archives of Oral Biology,* 18:765–770, 1973.

(4) Loesche, W. J., "Chemotherapy of Dental Plaque Infections," *Oral Science Reviews,* 9:65–107, 1976.

(5) Dawes, C., G. N. Jenkins, and C. H. Tonge, "The Nomenclature of the Integuments of the Enamel Surface of Teeth," *British Dental Journal,* 115:65–68, 1963.

(6) Bowen, W. H., "Nature of Plaque," *Oral Science Review,* 9:3–15, 1976.

(7) Volpe, A. R., et al., "Antimicrobial Control of Bacterial Plaque and Calculus and the Effects of these Agents on Oral Flora," *Journal of Dental Research,* 48:832–841, 1969.

(8) Beiswanger, B. B., O. P. Sturzenberger, and B. W. Bollmer, "Clinical Effect of an Antibacterial Mouthwash on Dental Plaque and Gingivitis," (abstract), *Journal of Dental Research, Special Abstract Supplement (International Association for Dental Research),* 55:146, 1974.

(9) Gomer, R. M., et al., "The Effect of Oral Rinses . . .," *Journal of the American Society for Preventive Dentistry,* 1:6–7, 12, 55, and 58, 1972.

(10) Lobene, R. R., and P. M. Soparkar, "The Effect of an Alexidine Mouthwash on Human Plaque and Gingivities," *Journal of the American Dental Association,* 87:848–851, 1973.

(11) Shipman, B., E. Cohen, and R. S. Kaslick, "The Effect of a Urea Peroxide Gel on Plaque Deposits and Gingival Status," *Journal of Periodontology,* 42:283–285, 1971.

(12) Schroeder, H. E., T. M. Marthaler, and H. R. Muhlemann, "Effects of Some Potential Inhibitors on Early Calculus Formation," *Helvetica Odontologica Acta,* 6:6–9, 1962.

(13) Kraus, F. W., "The Microbiology of the Oral Cavity and Its Systemic Significance," *Dental Clinics of North America,* 2:309–324, 1958.

7. *Oral malodor.* Oral malodor, also commonly known as "bad breath," "foul breath," or "halitosis," is not new or exclusive to modern times, nor is the plethora of preparations used to overcome it. Through the ages, attempts at elimination or masking of oral malodor have ranged from the chewing of odoriferous substances such as berries, perfuming, administration of enemas, smoking flavored cigarettes, and tongue scraping, to the more recent practice of instituting hygienic measures using various cosmetic preparations, such as odoriferous mouthwashes and gargles, and lozenges. Some of the products employed contain antimicrobial and other active ingredients for which therapeutic claims are made in addition to cosmetic claims.

The universal prevalence of oral malodor indicates that to have some degree of malodor is a normal human trait and is not evidence of the existence of any pathologic state. The assumption that oral malodor is associated with certain diseases states is scientifically incorrect. The presence of oral malodor is not indicative of the existence of systemic or oral disease and of the need for unsupervised self-treatment with medicated products. Ketone-like breath of diabetes, which is sweet and pleasant, is not a true oral malodor. In much of the older medical literature, associations between oral malodor and certain systemic diseases generally have been established in hospital environments. Since such an environment does not necessarily assign much importance to oral hygienic measures, it is not surprising that many hospitalized patients may manifest foul breath irrespective of the disease for which they are confined.

Since very few, if any, individuals can self-determine whether they have oral malodor (Ref. 1), the fear that failure to promptly institute medicated mouthwash usage may delay the treatment of a serious disease entity is unfounded. Unless a social contact informs an individual that he or she has malodor, the individual may be unaware of its presence. The presence of malodor ordinarily is not indicative of the existence of a pathologic state and results in no physical harm to a subject.

The Panel concludes that claims in the labeling of many oral health care products intended to overcome mouth odors are therapeutic claims and that most mouth odors are not associated with symptoms of pathologic processes requiring the need for medicated oral health care products. It is obvious that there may be differing opinions on this point between a product's sponsor and the Panel. It is the consensus of the Panel, therefore, that a detailed discussion of oral malodor should be a part of this document. The reason for this is so that the facts and reasoning upon which the Panel's recommendations concerning the use of products for suppression of malodor are based will be understood and recorded.

a. *Factors causing oral odors.* Oral odors can be classified according to their source. They may arise from systemic or local (i.e., nonsystemic) conditions or a combination of both. Both the systemic and local conditions can be due to internal (intrinsic) or external (extrinsic) causes. Examples of intrinsic systemic causes are the ketonic breath of diabetes mellitus, the urine-like malodor of uremia, and suppurative processes of structures of the upper and lower air passages and lungs. Examples of causes of extrinsic systemic malodors include ingestion of onion, garlic, wines and other alcoholic beverages, volatile drugs, and other odoriferous substances. The term "oral malodor" is nonspecific and ordinarily implies that the mouth odor is unpleasant and offensive, irrespective of etiology. Not all mouth odors are necessarily unpleasant and a distinction should be made between those that are offensive and can rightfully be classed as malodors and those that are not.

The frequency with which mouth odors due to systemic diseases appear in the population at large is dependent on the frequency of occurrence of the disease states that produce them. The frequency of these odors could perhaps be estimated from epidemiological data. Diabetes is one of the more common systemic diseases which can taint the breath with a sweet odor, since it is due to the exhalation of ketones. The odor is not necessarily unpleasant and offensive. Other systemic disease states, such as uremia, which is accompanied by a urine-like oral breath odor, and suppurative broncho-pulmonary diseases, are relatively less common. A sweet-smelling breath, or a urine-like breath, is, therefore, not a typical oral malodor. Odor resulting from suppurative pulmonary diseases can be disagreeable and offensive and classed as a malodor.

It should be noted that persons who have mouth odor due to systemic diseases are generally aware of their disease state. Also, the appearance of mouth odor is not the first symptom of that disease state but generally ensues after the disease is established or appears simultaneously with the major disease symptoms. To the Panel's knowledge there is no plethora of reports in the medical and dental literature of any significant number of cases in which mouth odor was an early diagnostic sign that established the presence of a systemic disease entity.

The concept that stomach odors taint the breath is false. The esophagus is a collapsed tube that communicates with the oral cavity only during swallowing, belching, or regurgitation (Refs. 2 through 7). Normal lung air does not contribute to mouth odors except in smokers or in those who have consumed alcoholic beverages or ingested

odoriferous foods such as garlic or volatile drugs such as paraldehyde that yield volatile byproducts which are excreted by the lung (Ref. 8). The contribution to oral odors by systemic conditions is minimal. A review of the literature indicates that more than 90 percent of all oral malodors are due to local oral conditions in the mouths of healthy persons (Refs. 3, 4, and 9). The remaining 10 percent of cases are due to extraoral causes of nonpathologic origin. Of these, most of the odors are due to volatile aromatic compounds circulating in the blood that are excreted into the lung air (Refs. 9 and 10).

It is estimated that upon arising in the morning, at least 9 out of 10 persons have oral malodor. Reilly (Ref. 5) has written, "Following sleep, nearly everyone has an unpleasant breath. The reduced activity of the tongue and the cheeks, together with the reduction in the flow of saliva, allow the bacterial flora of the mouth to be more active, resulting in an unpleasant breath."

In the past, substances causing oral malodors have been incorrectly assumed to consist of amines, fatty acids, and indoles (Ref. 11). By use of the gas chromatograph, a highly sensitive instrument capable of detecting various volatile substances to parts-per-billion ranges, it has been established that deadspace gases of the malodorous mouth consist mainly of minute traces of highly odoriferous volatile sulfur compounds. The most common and abundant of these are hydrogen sulfide, and methyl mercaptan. Traces of dimethylsulfides are also found (Refs. 12 through 15). The presence of volatile sulfur compounds detected by using the gas chromatograph has been correlated with the presence of nose-perceptible oral malodorous substances in test subjects. For example, if the subject had nose-perceptible oral malodor, the chromatograph showed the presence of volatile sulfur compounds. Absence of nose-perceptible malodor was accompanied by the absence of volatile sulfur compounds (Ref. 16).

Studies performed on the supernatant fluid of saliva, salivary sediment, and plaque have shown that microorganisms, in the presence of appropriate substrates, produce volatile sulfur compounds (Ref. 14). Sterile saliva has been shown not to produce putrefaction (Ref. 17) and malodor. The amines and indoles present have been shown to be nonvolatile, nonodorous substances. Volatility of a compound is a sine qua non requirement for its detection as a mouth odor causative agent (Ref. 11). The Panel, however, finds no data that support the concept that traces of volatile sulfur compounds formed by the resident oral flora in mouths of healthy persons are deleterious and injurious to the health of the individual. Likewise, it finds no data that justify a therapeutic use of antimicrobial agents for suppression of the formation of volatile sulfur compounds and other substances causing malodor.

b. *Role of microorganisms in the production of mouth odors.* The body has no mechanism for producing volatile sulfur compounds. Mammalian cells apparently do not possess the metabolic machinery (enzymes) to elaborate volatile sulfur compounds. Consequently, the production of volatile substances responsible for malodors in humans is dependent largely upon microbial metabolic processes. Reports of investigations have shown that microorganisms play an essential role in the production of oral malodor (Refs. 17 and 18). The incubation of sterile saliva produces no malodor. Yet, when whole nonsteril saliva is incubated, a shift of the bacterial population from gram-positive to gram-negative occurs with attendant malodor production (Ref. 18). However, these microorganisms are part of the indigenous oral flora and are known to be nonpathogenic under ordinary circumstances.

An important metabolic characteristic of certain gram-negative microorganisms found in the mouth is their ability to produce volatile sulfur compounds. One species of microorganism with pronounced metabolic capabilities to produce volatile sulfur compounds is fusobacterium, although other species such as peptostreptococcus may also be involved. All of these microorganisms are anaerobic and thus exist in areas of the mouth where the oxidation-reduction potential favors their survival. The principle areas where this occurs are the gingival crevices, interdental spaces, tonsilar folds, and the interpapillary crypts of the tongue (Ref. 17). The tongue has long been implicated as a reservoir of malodor-producing bacterial flora (Refs. 1 and 19).

It has been shown that glucose does not favor the production of malodor in incubated saliva (Refs. 17 and 20). Glucose, like other carbohydrates, favors fermentative metabolic pathways which produce nonodoriferous organic acid end-products. Amino acids, especially those containing sulfur, and short-chain peptides composed of sulfur-containing amino acids are the substrates leading to maximal putrefactive processes by the gram-negative microorganisms.

There are many reports of studies, both controlled and uncontrolled, on the etiology of local oral malodor. Most of these point to gram-negative organisms as the causative factors. In a 1949 study conducted by Morris and Read (Ref. 21), the use of a dentifrice, mechanical tongue prophylaxis, and an antibacterial mouthwash were found to be effective in reducing oral malodor. Water rinsing, however, was ineffective. However, this finding is not in agreement with findings found in other studies that indicate that water rinsing can be effective (Refs. 22 and 23). The antibacterial mouthwash used in the study of Morris and Read produced longer-lasting breath protection than tongue prophylaxis or brushing with a dentifrice. It was also noted in this study that the masking effect produced by flavoring agents contained in the mouthwash or dentifrice did not last, or mask, for more than 20 minutes, even though the protection against malodor continued for 3 hours following mouthwashing and 2 hours following toothbrushing.

c. *Elimination of mouth odors.* The control of local oral malodor depends upon its cause and may be accomplished by one or more of the following measures: purging, masking, neutralization, or bactrial inhibition. These measures are effective in controlling malodors of local origin and are generally not of value in controlling mouth odors of systemic origin, i.e. "onion" or "garlic breath."

(1) *Purging.* Malodors can be purged temporarily from the mouth by rinsing with water, brushing the teeth, using dental floss, or by eating a meal. The malodors are eliminated completely in some cases, reduced for a short time period in others, and in some cases not affected at all. The purging is due to a physical rinse-out or dislodgement of accumulated volatile sulfur compounds, food debris, or stagnant saliva, or to a reduction in the numbers of bacteria in the mouth. Dilution effect is common to most liquid preparations or products used to attempt to eliminate malodor.

(2) *Masking.* Local oral malodors may be masked by introducing a new, more pleasant odor into the mouth. This masking effect usually lasts only as long as the masking agent remains in the mouth at perceivable levels, generally from 15 ot 20 minutes in duration (Ref. 21).

(3) *Chemical neutralization.* Some agents react chemically with malodorous volatile compounds and form insoluble nonodorous products, usually nonvolatile sulfides. Chemical

neutralization is dependent upon how long the neutralizing agent lingers in the mouth, the quantity of malodorous material to be neutralized, and how quickly the malodor-causing chemicals are being remade. Chemical neutralization provides a longer-term local antimalodor effect than purging or masking. It may be prolonged further if accomplished by bacterial inhibition.

(4) *Bacterial inhibition.* Because certain strains of bacteria may cause oral malodor, inhibiting their metabolism or enzymatic activity or killing them may result in a temporary deodorizing effect. A longer term of action is apparent when the malodor is due to bacterial action and an antimicrobial agent is used. The effect persists even after the effects of purging and masking have been dissipated if they have also been used simultaneously. (Ref. 21). However, after meals and overnight sleeping the bacteria, having been mostly inhibited, will usually return to their original numbers and metabolic activities.

Because oral malodor is caused mainly by gram-negative anaerobes, only antimicrobial ingredients known to be effective against the causative organisms are effective in suppressing the malodor. However, agents that may be effective in one person may not be effective in another due to variations in the susceptibility of the microorganisms to the agent. Theoretically agents which preferentially inhibit or kill gram-negative anaerobes should be more effective in controlling oral malodor. Whether or not this is always the case is not known. There is ample evidence that the microbicidal effects of the antimicrobial agent are partial and incomplete and all the microorganisms are not killed by one application of the antimicrobial agent. The malodor due to bacterial action returns after the antimicrobial agent loses its effect and the microorganisms again begin to proliferate. In order to obtain a sustained effect, the user would have to reapply the ingredient repeatedly over 3- or 4-hour periods as long as the malodor persists (Ref. 21). The Panel does not consider this a judicious practice and does not recommend the unsupervised use of medicated oral health care products, particularly those containing antimicrobial agents, when there are no symptoms and when there is no evidence of the presence of a pathologic process. The Panel emphasizes that mouth odors without the presence of symptoms are not indicative of the existence of pathologic states and the use of antimicrobial and other therapeutic agents for their elimination is unwarranted.

d. "*Malodor testing.*" Various techniques have been divised for malodor testing. Although there may be variations among the techniques depending upon the subject population, investigators, location, purpose of the study, etc., most "malodor tests" follow a similar general protocol. Mouthwash formulations intended to control local oral malodor are tested in populations composed of normal subjects. Since most subjects exhibit oral malodor early in the morning and before the institution of hygienic measures, testing is done at this time. The subjects rinse with a mouthwash or a water rinse as a control. Expert judges, selected for their ability and consistency in scoring the intensity of oral malodor according to a pre-determined scale, sniff the breath of the test subjects before rinsing and at selected time intervals thereafter. The results are then analyzed and compared with effects of the water control rinse. Such testing is useful for demonstrating the relative effectiveness of a mouthwash compared to a water control rinse, the time period during which the mouthwash protects the oral cavity against oral malodor, and the relative pleasantness or unpleasantness of the subjects' breath before and after rinsing. Obviously such testing is in no way related to testing of the effectiveness and safety of a product for treatment of symptoms of pathologic processes causing sore mouth or sore throat. The Panel is unaware of any valid data concerning the relationship between sore mouth, sore throat, or both, and the presence or suppression of oral malodor. The "malodor test" is included in this discussion merely to indicate that such a test is in use primarily for evaluation of cosmetics and that the Panel considers it of little or of no value in the evaluation of antimicrobial or other therapeutic activity of oral health care products used to treat sore mouth, sore throat, or both.

The concept that some microorganisms present in the oral flora may play a beneficial role and help maintain a healthy state of the mouth has not, to the Panel's knowledge, been propounded, but certainly merits mention and consideration in this document. It is not out of the realm of possibility that certain nonpathogenic microorganisms play a contributory role in the self-cleansing process with the oral cavity is naturally endowed. Should this be the case the elimination of these microorganisms with medicated products would indeed be irrational.

In summary then, a review of the literature and the Panel's experience in laboratory and clinical research on oral malodor supports a local, oral origin for most oral malodors. In the majority of cases, the odors are due to traces of highly odoriferous, volatile sulfur compounds. These compounds are elaborated by the resident bacterial flora in the mouths of health persons. The microorganisms that have the metabolic pathways to elaborate volatile sulfur compounds in the oral cavity are mostly of the gram-negative nonpathogenic anaerobic variety. No relationship between the presence of these gram-negative organisms in the mouth and throat and diseases causing sore throat and sore mouth or other local or systemic diseases has been established. Normal lung air does not contribute to true oral malodor of local origin nor does the gas in the stomach. The stomach, for anatomic and physiologic reasons, is closed to the oral environment, except during swallowing and belching. The Panel considers products intended for elimination or suppression of mouth odor of local origin in healthy persons with healthy mouths to be cosmetics unless they contain antimicrobial or other drug ingredients. The Panel is mindful of the fact that the Federal Food, Drug, and Cosmetic Act indicates that articles that are cosmetics, but which are also intended to treat or prevent disease or to affect the structures of the human body, are drugs as well as cosmetic and must comply with both the drug and cosmetic provisions of the law and regulations (Ref. 24). Claims for the suppression of mouth odors using medicated oral health care products that are linked to a drug action, i.e. antimicrobial action, are drug claims. The Panel considers such drug claims to be Category II drug claims.

It is the consensus of the Panel that the use of OTC mouthwashes to control oral malodor is simply determined by an individual's need for social acceptance or personal oral gratification and is not mandated by the need to relieve symptoms of a pathologic state.

References

(1) Haggard, H. W., "Why Other People Smell," *Hygeia,* 19:12–14 and 60, 1941.

(2) MacDougall, J. L., "Halitosis," *University College Hospital Dental Journal,* 15:34–36, 1951.

(3) Prinz, H., "Offensive Breath, Its Causes and Its Prevention," *Dental Cosmos,* 72:700–707, 1930.

(4) Prinz, H., and S. S. Greenbaum, "Diseases of the Mouth and Their Treatment: A Text-book for Practititioners and Students

of Medicine and Dentistry," 2d Ed., Lea and Febiger, Philadelphia, pp. 92–102, 1939.

(5) Reilly, E. B., "Halitosis," *New Zealand Dental Journal,* 59:129–132, 1963.

(6) Snyder, M. A., "Fetor ex Or," *Penn Dental Journal,* 43:92–94, 1941.

(7) Spouge, J. D., "Halitosis: A Review of Its Causes and Treatment," *Dental Practitioner and Dental Record,* 14:307–317, 1964.

(8) Curby, W. A., "An Evaluation of the Contribution of Lung Air to Total Oral Odor," *Journal of the Society of Cosmetic Chemists,* 15:541–547, 1964.

(9) Herxheimer, A., et al., "Halitosis and Its Management," *Drug and Therapeutics Bulletin,* 7:79–80, 1969.

(10) Sulser, G. F., R. H. Brening, and L. S. Fosdick, "Some Conditions that Effect the Odor Concentration of Breath," *Journal of Dental Research,* 18:355–359, 1939.

(11) Tonzetich, J., et al., "Volatility as a Factor in the Inability of Certain Amines and Indole to Increase the Odour of Saliva," *Archives of Oral Biology,* 12:1167–1175, 1967.

(12) Blanchette, A. R., A. D. Cooper, and W. J. Tarbet, "Quantification and Evaluation of Volatile Sulfur Compounds in Mouth Air," (Abstract 142), *Journal of Dental Research,* 55:90, 1974.

(13) Tonzetich, J., "Direct Gas Chromatographic Analysis of Sulphur Compounds in Mouth Air in Man," *Archives of Oral Biology,* 16:587–597, 1971.

(14) Tonzetich, J., and R. C. Kestenbaum, "Odour Production by Human Salivary Fractions and Plaque," *Archives of Oral Biology,* 14:815–827, 1969.

(15) Tonzetich, J., and V. J. Richter, "Evaluation of Volatile Odoriferous Components of Saliva," *Archives of Oral Biology,* 9:39–45, 1964.

(16) OTC Volume 130099.

(17) McNamara, T. F., J. F. Alexander, and M. Lee, "The Role of Microorganisms in the Production of Oral Malodor," *Oral Surgery, Oral Medicine, Oral Pathology,* 34:41–48, 1972.

(18) Berg, M., and L. S. Fosdick, "Studies in Periodontal Disease: II. Putrefactive Organisms in the Mouth," *Journal of Dental Research,* 25:73–81, 1946.

(19) Massler, M., R. D. Emslie, and T. E. Bolden, "Fetor ex Ore: A Review," *Oral Surgery, Oral Medicine, Oral Pathology,* 4:110–125, 1951.

(20) Berg, M., D. Y. Burrill, and L. S. Fosdick, "Chemical Studies in Periodontal Disease: III. Putrefaction of Salivary Proteins," *Journal of Dental Research,* 25:231–246, 1946.

(21) Morris, P. P., and R. R. Read, "Halitosis: Variations in Mouth and Total Breath Odor Intensity Resulting from Prophylaxis and Antisepsis," *Journal of Dental Research,* 28:324–333, 1949.

(22) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, p. 309, 1975.

(23) OTC Volume 130149.

(24) "Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration," Food and Drug Administration, Publication No. (FDA) 79–1042, p. 50, 1979.

8. *Quaternary nitrogenous cationic antimicrobial agents.* The quaternary nitrogenous cationic agents manifesting antimicrobial activity evaluated by this Panel fall into several principal chemical groups.

a. *The quaternary ammonium compounds.* In these, the four hydrogen atoms of the positively charged ammonium ion are replaced by various organic radicals. The trivalent nitrogen atom of ammonia is converted to a pentavalent state capable of forming four covalent bonds and one positively charged ionic bond; the process is referred to as quaternization. These derivatives form bases which, when dissolved in water, yield a positively charged quaternary-substituted ion and a hydroxyl ion. These bases form salts with various acids, the most common of which in OTC products are hydrochloric and hydrobromic acid. When dissolved in water, hydrochloride or hydrobromide salts derived from substituted ammonia yield a positively charged ammonium ion and a negatively charged chloride or bromide ion. The cation manifests the antimicrobial properties. Benzethonium chloride is an example of such a compound.

b. *The pyridinium compounds.* In the pyridinium compounds the trivalent nitrogen atom in pyridine is converted to a pentavalent state with four covalent bonds and a positive ionic bond. When dissolved in water, a base forms which ionizes into a pyridinium ion and an hydroxyl ion. As is the case with substituted ammonium derivatives, the bases form salts with acids, usually hydrochloric or hydrobromic acids, and these are referred to as "pyridinium salts." The salts ionize into a pyridinium ion, which is positively charged, and a chloride or bromide negatively charged anion. Cetylpyridinium chloride is an example of such a compound. The hydrogen atom on the nitrogen atom of the positively charged pyridinium ion is substituted by an aliphatic (straight chain) or aromatic (benzene ring) radical. The cation manifests antimicrobial activity similar to the quaternary ammonium ion.

c.. *The quinolinium compounds.* In these, the trivalent nitrogen atom of quinoline is converted to a pentavalent state to form quinolinium derivatives. Substitutions with aromatic and aliphatic radicals may be made on the nitrogen atom as is the case with the ammonium and pyridinium derivatives. A methyl group on the 2 position of the quinoline nucleus yields a series of derviatives, called quinaldinium derivatives, when the nitrogen atom is quaternized. Quinaldinium is a base that dissolves in water to yield the quinaldinium ion, which is positively charged, and a hydroxyl ion. the quinaldinium bases form salts with acids which ionize into the quinaldinium ion and an anion. Dequalinium chloride is an example of an antimicrobial agent evaluated by the Panel falling into this category.

These three types of compounds all have one characteristic in common, i.e., they have one or more "quaternary" nitrogen atoms in their structures. For this reason, they are frequently called "quats." Many of them reduce surface tension and manifest various degrees of antimicrobial activity. The chemical behavior and biologic activities of the ammonium, pyridinium, and quinaldinium compounds are similar in most respects, so much so that some clinicians fail to make a distinction between the various types of compounds and refer to all of them as "quaternary ammonium compounds." All form salts with hydrochloric or hydrobromic acid, as does ammonia, and all salts are ionized when dissolved in water into "quaternary" nitrogenous positively charged cations and anions. The ability to substitute various organic radicals on the nitrogen atoms allows for the synthesis of a large group of variants. A large number of these variants has been prepared and tested for antimicrobial activity. The number that is clincially useful, which has been prepared from the large number of variants, is small. This Panel has evaluated only benzalkonium chloride, benzethonium chloride, cetyl benzalkonium chloride, domiphen bromide, cetalkonium chloride, and dequalinium chloride.

The nitrogenous cationic agents are characterized by a structural balance between one or more water-repelling (hydrophobic) groups and one or more water-attracting (hydrophilic) groups. It has been shown in the case of the substituted ammonium derivatives that in order to have pronounced antimicrobial activity one substituent must be a long alkyl (straight chain) radical of 12–16 carbon atoms, one substituent must be one short aromatic substituted alkyl group (a benzene ring on a short straight chain of several carbon atoms), and the remaining substituents must be two alkyl groups (straight chain of one or more carbon atoms such as methyl or ethyl groups). The long carbon chain may be modified by adding aromatic groups or hydrogen atoms. The long carbon chain confers lipophilic-hydrophobic properties and acts in a manner similar to a fatty acid. It is hydrophobic and oriented into a lipid phase of a water-lipid interphase.

The nitrogen atom is postiviely charged, hydrophilic, oriented into the water phase of a lipid-water interphase, and it acts like an ammonium ion. The pyridinium and quinolinium derivatives, likewise, have hydrophobic-lipophilic groups by virtue of their aromatic structures. They also have a long carbon atom chain substituted for a hydrogen atom on the nitrogen atom and a hydrophilic group that results from the ionic activity of the quationized nitrogen atom. Thus, all three types must have one fatty-acid type of radical as a substituent on the nitrogen atom.

The quaternary nitrogen cationic derivatives are capable of altering the physiochemical relationships of liquid-liquid or gas-liquid interphases. Some cause a marked reduction of surface tension. In some cases the surface tension is reduced to as low as 37 dynes per square centimeter (dyn/cm^2) at 25° C. Substances that act in this manner are also referred to as "detergents" or "surface-active" compounds.

These compounds have characteristics that are common to the entire class of quaternary nitrogenous derivatives. The exact mechanism by which quaternary nitrogenous compounds exert their antimicrobial activity is not known. A number of mechanisms of action have been suggested: (1) They may exert their antimicrobial activity by disrupting the microbial cell membrane and allowing the microbial cytoplasm, enzymes, or other substances to diffuse out of the cell; (2) they may act by dissolving the protective lipid films in the microbial cell membranes, since they are lipophilic; (3) they may act by denaturing certain proteins with which they combine on the surface of a cell; (4) they may inactivate microbial intracellular enzymes; and (5) they may interfere with the activity of enzymes involved in the transport of chemicals across cell membranes. Any one of the above or a combination of two or more mechanisms may be responsible for the antimicrobial activity. The cells of the host can also be affected by these substances, as is the case with other antimicrobial agents, but available data indicate they do so to a lesser degree in most cases. There is no well-defined correlation between the surface-tension-reducing activity of these compounds and their antimicrobial activity. Many substances that cause a pronounced decrease in surface tension possess no significant antimicrobial activity. The quaternary nitrogenous agents manifest a high degree of absorbability. They are readily absorbed by activated charcoal, silica gel, and to a lesser degree, by agar and other absorbents. A similar degree of absorbability is believed to occur on the cell surface, altering metabolic activity.

The antimicrobial activity of quaternary nitrogenous agents is due to the aforementioned physiochemical attributes. On the other hand, these same attributes also account for the inactivation of quaternary nitrogenous agents and cause them to be ineffective. They are readily absorbed or acted upon by other agents present in an infected area, wound, or culture medium. They are inactivated by proteins, pus, debrided cells, blood, rubber, cotton, wool, and even glass, plastic, and other substances capable of absorbing them. Soaps, in particular, since they are anionic detergents, deactivate quaternary nitrogenous compounds when only small traces are present. The anionic antimicrobial agents cannot be formulated with the cationic agents since each type deactivates the other. In addition, their activity is dependent upon environmental temperature and pH. They are ineffective at near-neutral pH but their activity is increased as pH increases. Many manifest their greatest activity at a pH 8 or above. This is a greater pH than that of the tissues. The pH of tissue fluids in infected areas is usually acidic and ranges from 5 to 7. The antimicrobial activity increases as environmental temperature increases.

The majority of quaternary nitrogenous compounds are bacteriostatic rather than bactericidal. They are more active against gram-positive bacteria than gram-negative organisms. This particular attribute of variation in antimicrobial activity casts doubt on their value and effectiveness as antimicrobial agents in the mouth and throat where gram-positive bacteria abound. The "quats" are nonspecifically absorbed to the cell membrane and the unprotected cell menbrane is more sensitive to their action than the protected cell membrane, which probably accounts for differences in sensitivity. The differences in sensitivity between gram-positive and gram-negative organisms is probably due to greater absorbability of the "quats" to the gram-positive organism and the ability of the agent to pass into and beneath the cell wall of the gram-positive microorganism.

Strains of *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* are particularly resistant to these antimicrobial agents. Most bacterial spores remain viable even after prolonged contact with solutions of quaternary nitrogenous compounds. Their usefulness in combating fungal infections has not been established. The fungicidal activity of the "quats" is less than their bactericidal activity. Most of the quaternary nitrogenous derivatives of this type are not virucidal. When they are used as skin disinfectants, some form a film on the skin under which bacteria remain viable.

Cationic agents appear to possess a low order of systemic toxicity in animals and humans. Poisoning from oral ingestion has been reported. The toxicity reported appears to be related to the surfactant nature of the "quats." Rabbits can tolerate 1.2 cubic centimeter (cm^3) of a 1-percent benzalkonium chloride solution subcutaneously or intraperitoneally for days without signs of adverse effects. Chronic toxicity studies or various compounds in animals reveal weight loss, loss of appetite, etc. Prolonged contact with the skin and mucous membranes produces irritation. In rabbits, the highest concentration of benzalkonium chloride that could remain in contact with the skin for 24 hours without signs of irritations was 0.1 percent. The concentrations in which the "quats" are used are low so that irritation usually is not a serious problem. As is the case with other agents, the "quats" can bind with protein and act as haptenic antigens and produce sensitization. However, this has not been a common occurrence and the incidence of sensitivity reactions has been low.

The safety of quaternary nitrogen compounds for use in the oral cavity is difficult to evaluate because the available data concerning application on the mucous membranes of the mouth and throat is scant. Data from controlled studies on the permeability through the membranes, the degree of systemic absorption, degree of irritancy, and sensitizing potential after application to the oral mucous membranes are not available, and a definitive judgement cannot be made at this time. Data on absorption through the mucous membranes, blood levels, and biotransformation likewise are not available. Toxicity studies have generally been limited to animal species; little data are available on the effects of chronic use on people. Controlled clinical toxicity studies are, in most cases, lacking. There is a need for additional data on irritation and sensitization from chronic exposure on the oral and pharyngeal mucous membranes in order to properly evaluate these ingredients, particularly with regard to safety.

The quaternary nitrogenous compounds are ionized. Ionized substances are not readily absorbed

through the lipoid barriers of the cell nor do they penetrate the blood-brain barrier; therefore, one would expect these compounds not to be absorbed in any great quantity. On the other hand, to what degree the lipophilic pole present on the molecule enhances their lipid solubility and adsorbability is not known. Were they not soluble, they would not penetrate the cell of the microorganisms or cells of the host. Quaternary nitrogenous compounds, if absorbed, could act as automatic ganglionic blocking agents. They may also manifest a curariform action. It has been suggested that a possible use for certain of these compounds would be as ganglionic blocking agents. Another possible use suggested is as anticholinergic agents. The quaternary nitrogenous compounds manifest no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

Effective cationic agents have the following advantages over other antimicrobial agents for use as antiseptics: (1) They are used in relatively low concentrations and are nonirritating to tissues in such concentrations: (2) they have a rapid onset of action; (3) they "wet" and penetrate tissue surfaces quickly and readily; and (4) they possess detergent emulsifying and keratolytic actions.

This disadvantages are (1) they are irritating in high concentrations; (2) they vary in the spectrum of antimicrobial activity; (3) they are inactivated by anionic agents, proteins, various adsorbents, etc., (4) data on toxcity, both local and systemic, and acute and chronic, in humans are scant; (5) the in vitro data do not correlate with and provide an index of in vivo effectiveness; (6) they are of limited use as virucidal and fungicidal agents; and (7) little is known of their actions on protozoan type organisms.

9. *Volatile oils.* A group of oils, obtained from botanical sources often referred to as ethereal of essential oils, contains a miscellaneous number of ingredients that have been used for therapeutic purposes. They have been used empirically and are considered to be effective antimicrobial agents in spite of inadequate data to support this contention. The volatile oils are mixtures of various types of chemicals whose composition is inconsistent and varies with their source. For this reason, a general statement is made here concerning volatile oils.

The volatile oils are obtained from various plants by distillation or by pressure. They are found in different types of fruits or flowering parts of plants, all of which are widely distributed throughout the plant kingdom. They are not obtained from one single source. Most are strongly odorous and, therefore, are used as perfumery to conceal disagreeable odors and tastes in medicine. They must be distinguished from the fatty or fixed oils which are nonvolatile.

Most volatile oils are mixtures that have terpenes as their commonest constituents. Some oils contain only terpenes, depending upon the source. Terpenes are hydrocarbons of the aromatic series that possess the general formula $(C_5H_8)_n$. Some terpenes are combinations of dihydrobenzene with propyl and methyl groups and at least a dozen terpenes of this type are known. Another group of hydrocarbons found in these oils is known as the sesquiterpenes, while a few are diterpenes. Some volatile oils consist of these hydrocarbons exclusively, but most of them contain some oxidized aromatic substances such as phenols, ketones, aldehydes, acids, and components of these substances. For instance, some contain camphor, thujone (from oil of absinthe), sabinol oil, safro, thymol, eucalyptol, myristicine, and vanillin.

Many of these oxidized products crystallize out when the volatile oils are cooled or are left standing. The resulting solids are known as stearoptens, while the remaining fluid is called eleopten. The constitutents of the oils that contain oxygen in their molecular structures are not as volatile as the pure hydrocarbons. The odor is due mainly to the oxidized substances. A few oils contain nitrogenous bodies, generally in the form of cyanides. On the other hand, the majority of volatile oils obtained from the curuciserae species contain sulfur bodies which give them a pungent, disagreeable odor quite different from that of the other oils.

The volatile oils are generally clear, colorless liquids, although some are green or blue in color. After long standing they may become discolored, decompose, and become acidic in reaction resulting from the formation of resins. Some are light, sparking fluids. Many of the plants from which the volatile oils are obtained possess other active constitutents, such as bitters. Many of the preparations used in therapeutics are formed not from the distilled oils but from crude parts of the plants. In many cases, the oil is not the only active principle present in the plant.

Strong solutions of volatile oils have a hot, burning taste and if kept in the mouth cause redness and irritation of the mucous membranes, although some of them induce a sense of coolness at first. At the same time the organs of smell are affected by these oils because most possess characteristic odors. Irritation of the mouth leads to reflex secretion of saliva which is often very profuse. When used in the mouth or elsewhere the antiseptic action of the oils may have a beneficial effect in some conditions.

In the stomach the oils cause the same sensation of warmth. The appetite may often be increased and the feeling of distension after meals is often relieved. Some cause the release of quantities of gas. Substances which produce these in the stomach are known as carminatives, and many explanations of their action have been offered. In the intestines small quantities generally increase movements while larger quantities decrease them. Sometimes the bowel is relaxed due to reflexes arising from interaction of the oils on the stomach. In practice, they often relieve intestinal flatulence and distension and lessen the spasms which cause colic.

Many of the terpenes are oxidized to phenols in the body and then excreted in the urine. For the most part, they combine with glucuronic acid and sulphuric acid. They leave by way of the expired air and impart an odor to the breath. In the course of excretion, some of the oils may cause irritation of the lungs. Some of the oils are employed as expectorants to increase bronchial secretions.

The volatile oils all possess some antimicrobial activity which is believed to be due to their volatility and solubility in liquids. This enables them to penetrate readily into the protoplasm. Many of them appear to be more germicidal than phenol under favorable circumstances. They are generally too insoluble in water to be employed easily for medicinal purposes, and this also limits their usefulness as antimicrobials in the highly aqueous environment of the mouth. When some are applied to the skin they cause redness, itching, and warmth resulting from local dilation of the vessels. This dilation may be due to penetration of the oil into the cutaneous arterioles, veins, or to local reflex effects from the irritation of the terminal sensory nerves. When painted on the mucous membranes, such as those of the eye, nose, or on wounds, the volatile oils cause a similar type of irritation which is characterized by redness, congestion, and smarting. Some are used as counterirritants on the skin. The Panel does not believe that the counterirritant effect is of any therapeutic value on the mucous membranes. It is the consensus of the Panel that individual pure ingredients such as thymol, eucalyptol,

and menthol extracted from the volatile oils are more effective, safer, and are more easily evaluated than these heterogenous mixtures of inconstant composition. The Panel feels that the volatile oils may be used as flavorants or to impart pleasant odors to a product.

10. *Absorption, distribution, and metabolism.* In addition to their local cytotoxic effects, many topically applied antimicrobial agents and disinfectants may manifest systemic toxic effects because they are absorbed from the mucous membranes, circulate in the blood, and affect susceptible target tissues and organs. Absorption readily occurs from the mucous membranes of the mouth, pharynx, and from the stomach, if these agents are swallowed. This has led to a further limitation of the use of certain effective antimicrobial agents. These systemic effects may not necessarily be due to the qualities which render such drugs antimicrobial. The systemic actions may be attributed to other pharmacologic or chemical properties of a drug. Systemic reactions may be avoided by exercising care in selecting a drug and by avoiding its misuse.

The manner in which an antiseptic is absorbed, its rapidity of absorption, distribution in the body, and systemic toxicity vary with each chemical and pharmacologic type and each individual compound. The mercurial derivatives, for example, are nephrotoxic; the chromates are likewise nephrotoxic; the phenols affect the central nervous system, etc. Antimicrobial agents, as is the case with most drugs, are metabolized by the liver or are excreted unchanged by the kidney if they are absorbed. Some are excreted into the intestine, particularly the colon. Some pass into the bile, and others pass into the sweat and into the milk of lactating women. The metabolic fate of each systemically absorbed drug is considered in the individual ingredient statements.

11. *Adverse reactions.* The adverse effects of antimicrobial agents contained in oral health care products merits consideration from two standpoints: (1) From the standpoint of short-term therapy when used to treat pathologic states that cause sore mouth and sore throat and (2) from the standpoint of long-term use for cleansing, elimination of mouth odors and other purposes when no pathologic state or symptoms of a disease exist. Most of the mouthwashes, rinses, and gargles evaluated by the Panel that contain antiseptics are recommended for long-term use on a daily basis or oftener. Some are used by consumers for years at a time. In many cases, there is a paucity of data on the remote adverse effects that may ensue from long-term use of these ingredients. It is the belief of the Panel that such ingredients should not be used until their safety, following chronic long-term use, has been established.

The general aspects of adverse reactions from use of all OTC oral health ingredients evaluated by the Panel have been discussed previously. (See part II. paragraph E. above—Adverse Reactions.) There are, however, certain specific aspects pertaining to antiseptics that have been discussed in a general manner in that section which require further discussion and elaboration.

Topically active antiseptics kill or inhibit the growth of microorganisms but are also cytotoxic and may injure normal cells of the host and cause tissue destruction. They may irritate tissues, be corrosive, and cause ulceration and even sloughing of the mucous membranes and submucosal tissues. These local, irritating reactions may occur during short-term as well as long-term use. Sloughing has resulted from the use of certain phenolic compounds, overuse of peroxides and other oxidizing agents, certain iodophors, and combinations of the volatile oils.

Recently, Bernstein (Ref. 1) has reported oral mucosal white lesions associated with excessive use of a commercial mouthwash. He found that the excessive topical application of a mouthwash containing 25 to 26.9 percent alcohol, thymol, eucalyptol, methyl salicylate, menthol, benzoic acid, and boric acid, at a pH of 4.4, produced asymptomatic diffuse white mucosal lesions in two patients. He concedes that any one or a combination of several ingredients in this mouthwash, as well as the acid pH or tonicity, must be considered as possible factors in the etiology of the white lesions. Alcohol is a likely suspect in view of a previous report by Baer and Archard (Ref. 2). Bernstein indicates in his discussion that several reports concerning the adverse effects of mouthwashes appear in the literature. He quotes two articles, one by Kowitz, Lucatorto, and Cherrick (Ref. 3) and another by Fisher (Ref. 4). In these reports it is noted that the most common adverse effect is a stomatitis due to a primary irritant effect or hypersensitivity. This adverse effect is manifested by erythema, ulceration, or ipithelial sloughing. Essential oils, astringents, and antiseptics are usually implicated in the etiology of these reactions. They occur as isolated cases in persons who have idiosyncrasies or who are sensitive to the preparations. They note that the acute symptomatic responses are not necessarily correlated with abuse of the product. The pathogenesis of this type of reaction appears to be different from the two reported cases in which prolonged contact of a chemical was associated with asymptomatic, nonallergic white lesions (Ref. 1).

Bernstein (Ref. 1) further states that very few articles have been published documenting white lesions associated with mouthwashes or ingredients contained therein. Although sloughing white patches following the use of chlorhexidine mouthwash was reported by Flotra and colleagues (Ref. 5), whom he quotes in this article, a subsequent study failed to reveal increased thickness of the stratum corneum in biopsy specimens taken from human subjects who rinsed with chlorhexidine (Ref. 6). In the cited article, Baer and Archard (Ref. 2) observed the development of white lesions of the gingiva and alveolar mucosa following the chronic and excessive topical application of isopropyl alcohol. Histologic sections revealed coagulative hyperparakeratosis and acanthosis. Discontinuation of the alcohol resulted in remission of the lesion. How many local reactions that never come to the attention of a manufacturer or sponsor of a product or the FDA will never be known because few physicians or dentists take the time or trouble to report the occurrence of such lesions, particularly if they disappear when use of a product is discontinued. The various types of lesions that have occurred and been reported from local effects of these ingredients are discussed in the description of the various ingredients.

Most ingredients in mouthwashes can be absorbed from the mucous membranes of the mouth or throat, or the stomach if swallowed. Ferguson, Geddes, and Wray (Ref. 7) recently reported that short-term therapy with a providone-iodine mouthwash had an adverse effect on 16 healthy individuals after 2 weeks of use. Significant increases occurred in the total serum iodide, protein bound iodine, inorganic iodine, T3 resin uptake, total thyroxine, and free thyroxine index. The possibility of thyroid suppression following long-term use is also mentioned in this article. The systemic effects from short-term therapy, as well as long-term use of antiseptics in oral health care products are mentioned, if known, in each ingredient section outlined below. In many cases, particularly in the case of the more recently introduced

antimicrobial agents, such as the quaternary nitrogenous compounds, there is a paucity of data on chronic systemic toxicity in humans.

Data on the tumorigenic, mutagenic, and teratogenic effects of antiseptics when used in oral health care products on a daily basis or more often for years at a time are sparse. There is some evidence that phenol may act as a cocarcinogen, but it has not been shown to do so conclusively. Phenol still is available for OTC use in mouthwashes, rinses, and sprays and will continue to be until additional data becomes available.

Weaver, Fleming, and Smith (Ref. 8) studied 200 patients with squamous cell cancer of the head and neck and compared them to patients in the general surgery group on use of tobacco, alcoholic beverages, and mouthwash. Analysis disclosed that patients with cancer of the head and neck used significantly greater quantities of tobacco and alcoholic beverages and mouthwash than the control group. However, 11 patients with cancer of the head and neck had abstained from alcoholic beverages and tobacco, but each had used significantly more mouthwash than had patients in the general surgery group. Several brands of mouthwash have an alcoholic content of 14 to 28 percent. Weaver, Fleming, and Smith (Ref. 8) feel the alcohol in the mouthwash may be a causative agent. They also indicate that other possibly irritating substances are contained in mouthwashes. These include cetylpyridinium chloride, thymol, eucalptol, phenol, methyl salicylate, and boric acid. Weaver, Fleming, and Smith (Ref. 8) quote Kowitz, Lucatorto, and Cherrick (Ref. 3) who have reported epithelial peeling, mucosal ulceration, gingivitis, and petechiae in as many as 25 percent of those dental and dental hygiene students who used 20 mL of full-strength mouthwash for 5-second intervals twice daily throughout a 2-week period. These signs of acute inflammation disappeared when use of the mouthwash was discontinued. Weaver, Fleming, and Smith (Ref. 8) feel that chronic irritation from use of mouthwashes may be carcinogenic. All but one of the previously mentioned 11 patients who developed cancer had used mouthwash several times daily for more than 20 years. Most of them used a brand of mouthwash that contained 25 percent alcohol. These data on the case histories presented in their report suggest that a history of the use of a mouthwash should be included for outpatients with premalignant or malignant lesions of the oral cavity, as mouthwash may indeed be carcinogenic for susceptible individuals. To their knowledge, no previous study has included a history of patients using mouthwash in the study of the incidence of cancer of the head and neck. Alcohol, in the absence of tobacco, appears to be a weak carcinogen. If a mouthwash is weakly carcinogenic, a susceptible person using this substance while abstaining from alcoholic beverages and tobacco might be expected to develop a carcinoma at a more advanced stage. Weaver, Fleming, and Smith (Ref. 8) also point out that it is interesting that 9 of 11 patients with cancer from excessive use of mouthwash were women and that all 11 patients had cancer involving the oral cavity. This is consistent with the site and distribution by sex for previously unexplained squamous cell cancer of the head and neck region reported from other sources by other clinicians.

Wlodkowski, Speck, and Rosenkranz (Ref. 9) have indicated that povidone-iodine is capable of specifically altering the deoxyribonucleic acid (DNA) of living cells and inducing mutations in salmonella. Because of the known potential and the ability of a mutagenic substance to induce cancer in animals, this finding raises serious questions concerning safety of iodine as a topical disinfectant. The halogens, including iodine, are capable of reacting with nucleic acids and their constituents and affect DNA. Although all of the aforementioned comments do not establish the fact that these drugs can cause cancer, this aspect of tumorigenesis cannot be ignored and requires further study. The argument that no ill-effects have been reported from long-term use is without merit and means little. Chloroform had been used as a flavorant in OTC oral health are products for years. It was not until recently that its potential for producing carcinoma was verified and its use in OTC products no longer allowed.

Topically applied antimicrobial agents may also activate the T-type lymphocytes in the tissues and cause delayed type of sensitivity. This results in allergic contact dermatitis on the skin if the drug is distributed to the skin by systemic transport. They may also act on the T-lymphocyte system in the mucous membranes and cause stomatitis and other local ulcerations of the mouth, throat, and gums. Antiseptics may also cause allergic reactions of Type I involving IgE such as anaphylaxis, rhinitis, angioedema, etc. (See part II. paragraph E. above—Adverse Reactions.) If absorbed, systemic allergic reactions may occur.

The relationship of plaque formation and production of caries has not been definitely established. Should there be a definite relationship between antimicrobial activity in plaque and development of caries and should an antiseptic be indicated for prophylaxis, it is the feeling of the Panel that preparations that can be applied locally to the teeth, such as pastes or powders, are indicated. The Panel considers the periodic flushing of the entire oral cavity, which is not involved in cariogenic activity, with an antiseptic for prophylactic purposes is a procedure of doubtful rationality and one that should be discouraged.

References

(1) Bernstein, M. L., "Oral Mucosal White Lesions Associated with Excessive Use of Listerine Mouthwash: Report of Two Cases," *Oral Surgery, Oral Medicine, Oral Pathology,* 46:781–785, 1978.

(2) Baer, P. N., and H. O. Archard, "Factitial Disease of the Gingiva and Buccal Mucosa: Report of a Case," *New York State Dental Journal,* 40:33–36, 1974.

(3) Kowitz, G. M., F. M. Lucatorto, and H. M. Cherrick, "Effects of Mouthwashes on the Oral Soft Tissues," *Journal of Oral Medicine,* 31:47–50, 1976.

(4) Fisher, A. A., "Contact Stomatitis, Glossitis, and Cheilitis," *Otolaryngology Clinics of North America,* 7:827–843, 1974.

(5) Flotra, L., et al., "Side Effects of Chlorhexidine Mouthwashes," Scandinavian Journal of Dental Research, 79:119–125, 1971.

(6) Mackenzie, I. C., et al., "Two Years Oral Use of Chlorhexidine in Man: V. Effects on Stratum Corneum of Oral Mucosa," *Journal of Periodontal Research,* 11:165–171, 1976.

(7) Ferguson, M. M., D. A. Geddes, and D. Wray, "The Effect of a Povidone-Iodine Mouthwash Upon Thyroid Function and Plaque Accumulation," *British Dental Journal,* 144:14–16, 1978.

(8) Weaver, A., S. M. Fleming, and D. B. Smith, "Mouthwash and Oral Cancer: Carcinogen or Coincidence?," *Journal of Oral Surgery,* 37:250–253, 1979.

(9) Wlodkowski, T. J., W. T. Speck, and H. S. Rosenkranz, "Genetic Effects of Povidone-Iodine," *Journal of Pharmaceutical Sciences,* 64:1235–1237, 1975.

B. Categorization of Data

1. *Category I conditions under which antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

None.

Category I Labeling

a. *Indication.* The Panel did not classify any antimicrobial active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel did not place any indication in Category I. The Panel has proposed a Category III indication for oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

b. *Warnings*(1) *For all products containing oral health care antimicrobial active ingredients.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing oral health care antimicrobial active ingredients used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care antimicrobial drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

Boric acid
Boroglycerin
Camphor
Cresol
Ferric chloride
Meralein Sodium
Nitromersol
Potassium chlorate
Sodium dichromate
Tincture of myrrh

a. *Boric acid.* The panel concludes that boric acid is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boric acid (H_3BO_3) is also known as boracic acid or orthoboric acid. It occurs as a colorless or white powder or as scales or granules with a slightly bitter taste. It has a molecular weight of 61.844 and a melting point of 184° C.

One gram of boric acid dissolves in 18 mL of cold water or in 4 mL of boiling water. It also dissolves in 18 mL of cold alcohol, 6 mL of boiling alcohol, and in 4 mL of glycerol. Boric acid is used as a pharmaceutical necessity for buffering as well as for an active ingredient (Ref. 1). It is stable in air and incompatible with alkalis, carbonates, and hydroxides. Boric acid is prepared by the action of sulfuric acid on sodium borate.

A 2.5-percent solution of boric acid is said to be bacteriostatic, but not bactericidal. It is a mild topical astringent and drying agent with anti-inflammatory and antipruritic effects. In concentrations ordinarily used clinically, boric acid does not irritate or devitalize tissues (Ref. 2). It has been found that concentrations greater than 2 percent may inhibit phagocytosis, thereby negating a primary defense mechanism of the body against bacterial invasion (Ref. 3).

Elemental boron is an essential element for plant life, but this does not appear to be the case for animal life.

(1) *Safety.* The Panel concludes that boric acid is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Absorption of boric acid occurs readily from the mucous membranes of the mouth, throat, gastrointestinal tract, and from the lining of hollow viscera. It is also absorbed from the surface of the vagina, the lining of the conjunctival sac, from abraded or denuded skin, and from wounds (Ref. 4). The absorption of toxic doses may occur rapidly, yet toxic symptoms may be delayed for hours. Intact, healthy skin apparently acts as an effective barrier for boric acid (Refs. 5 and 6); however, there are differing opinions in the literature concerning this point (Refs. 7, 8, and 9). Seventy to 90 percent of an oral dose of boric acid is excreted in the urine unchanged. Only small amounts are found in the feces, saliva, and perspiration. Excretion of boric acid is not influenced by fluid intake but is significantly delayed by renal disease. About 50 percent of a dose is excreted within the first 12 hours, and the remainder is eliminated over a period of 5 to 7 days (Ref. 10). During chronic administration, elimination is slow. A plateau in urinary excretion usually is reached after 2 weeks (Refs. 5 and 6). Thus, there is a tendency for accumulation to occur with chronic use. There is a greater amount of boron in the brain when accumulation occurs, than at the site of treatment, especially wounds (Refs. 5 and 6). Large amounts are also found in the liver and the kidney. Kidney damage occurs when toxic doses are ingested.

The oral LD_{50} for dogs is greater than 1,000 mg/kg. The subcutaneous LD_{50} for guinea pigs is 1,200±80 mg/kg. In the mouse, the oral LD_{50} is 3,450 mg/kg. In the rat, the oral LD_{50} is 5,140 mg/kg.

The exact lethal dose of boric acid in humans is not known. Death has occurred from ingestion of less than 5 g in infants and from 5 to 20 g in adults. Amounts of this magnitude can be absorbed readily when boric acid solutions are used to irrigate closed cavities (Ref. 11). In a study of 100 cases of accidental poisoning, the overall fatality rate was 55 percent, but in infants under 1 year of age, 70 percent ended fatally (Ref. 12).

The symptoms of poisoning from boron derivatives are nausea, vomiting, diarrhea, and epigastric pain. Vomiting is often persistent and the vomitus and feces may contain blood. Hemorrhagic gastroenteritis may develop irrespective of the route of administration. Both the vomitus and stools have a blue-green color. Weakness, lethargy, headache, restlessness, irritability, tremors, and intermittent convulsions with subsequent depression of the central nervous system occur. Skin eruptions and kidney and liver damage have also been reported.

In 1962, 172 cases of boric acid intoxications with 89 deaths were compiled from the literature. In 53 cases, the drug had been used externally. Death occured in 23 of 30 children with diaper rashes (Ref. 13). The American Academy of Pediatrics has condemned this drug and recommended that its use be abandoned.

It is the consensus of the Panel that all OTC products containing boric acid and recommended for topical use on the mucous membranes of the mouth and throat likewise be condemned.

(2) *Effectiveness.* The Panel concludes that boric acid is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boric acid and its sodium salt have weak bacteriostatic and fungistatic activities. Neither the salt nor the acid is germicidal or fungicidal even in saturated aqueous solutions. A 2.5-percent aqueous solution will stop the growth of almost all forms of bacilli. They are not destroyed, however. The growth of the anthrax bacillus is inhibited, but is not halted when exposed to a 4-percent solution of boric acid. Furthermore, when removed from the boric acid solution anthrax bacilli once again begin to grow uninhibited (Ref. 14). Boric acid, therefore, is of

doubtful value as an antiseptic and is only suitable for bacteriostatic purposes. It has the advantage over other antimicrobial agents with bacteriostatic activity in that it induces very little irritation of wounds or delicate tissues such as the conjunctiva and mucous membranes of the eye, nose, mouth, throat, or even the gastrointestinal tract. Boric acid was, once upon a time, used as a preservative for foods, some medicines, and cosmetics. Its use for this purpose is now forbidden by law.

The mode of action of boric acid as a bacteriostatic agent is not known. Whether or not its effect is due to the hydrogen ion released from the acid is not known. Solutions of 0.3 percent inhibit putrefaction and decomposition, but do not inhibit the growth of pathogenic organisms.

The bacteriostatic effectiveness of boric acid varies with different types of bacterial cultures. It begins to manifest bacteriostatic activity at approximately a 1/20 saturated aqueous solution and does not appear to increase in activity after concentrations are 1/6 saturated.

Boric acid and sodium borate have no disinfectant properties. The chemically allied salt, borax ($Na_2B_4O_7$), is alkaline and also manifests bacteriostatic activity. Borax is less active than the acid, and it acts to some extent as a debriding agent due to its alkalinity.

(3) *Evaluation.* The Panel classifies boric acid, sodium borate, and borax as Category II from both the standpoint of safety and effectiveness as a topical antimicrobial agent in the mouth and throat. The reaons for this are because of their toxicity, since they are derived from boron, and because of their questionable bactericidal and disinfectant effects.

References

(1) "National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 776–777, 1975.

(2) Oster, K. A., "Chemotherapy of Bacterial Infections I: Antiseptics and Germicides," *in* "Drill's Pharmacology in Medicine," 4th Ed., edited by J. R. DiPalma, McGraw-Hill Book Co., New York, p. 1635, 1971.

(3) Novak, M., and W. I. Taylor, "Phagocyticidal and Antibacterial Action of Boric Acid," *Journal of the American Pharmaceutical Association (Scientific edition),* 40:428–430, 1951.

(4) George, A. J., "Toxicity of Boric Acid through Skin and Mucous Membranes," *Food and Cosmetic Toxicology,* 3:99–101, 1965.

(5) Pfeiffer, C. C., and E. H. Jenney, "The Pharmacology of Boric Acid and Boron Compounds," *Bulletin of the National Formulary Committee,* 18:57–80, 1950.

(6) Pfeiffer, C. C., L. F. Hallman, and I. Gersh, "Boric Acid Ointment: A Study of Possible Intoxication in the Treatment of Burns," *Journal of the American Medical Association,* 128:266–274, 1945.

(7) Mulinos, M. G., C. Connant, and E. Hauser, "The Toxicity of Boric Acid and the Clinical Implications of the Use of Borated Baby Powders," *Bulletin of the New York Medical College,* 16:92–101, 1953.

(8) Fisher, R. S., et al., "Boron Absorption from Borated Talc," *Journal of the American Medical Association,* 157:503.505, 1955.

(9) Fisher, R. S., "Intracytoplasmic Inclusions in the Pancreas Due to Boric Acid Poisoning," (Abstract), *American Journal of Pathology,* 27:745, 1951.

(10) Locksley, H. B., and W. H. Sweet, "Tissue Distribution of Boron Compounds in Relation to Neutron-Capture Therapy of Cancer," *Proceedings of the Society for Experimental Biology and Medicine,* 86:56–63, 1954.

(11) Ross, C. A., and J. F. Conway, "The Dangers of Boric Acid: Its Use as an Irrigant and Report of a Case," *American Journal of Surgery,* 60:386–395, 1943.

(12) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 7th Ed., Lea and Febiger, Philadelphia, pp. 694–695, 1970.

(13) Valdes-Dapena, M. A., and J. B. Arey, "Boric Acid Poisoning: Three Fatal Cases with Pancreatic Inclusions and a Review of the Literature," *Journal of Pediatrics,* 61:531–546, 1962.

(14) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 7th Ed., Lea and Febiger, Philadelphia, p. 808, 1970.

b. *Boroglycerin glycerite.* The Panel concludes that boroglycerin glycerite is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite is made by dissolving boroglycerin in glycerin. Boroglycerin is glycerin borate. It is also know as glycerite of boric acid, glyceritum boroglycerin, and glyceritum acidi borici. Boroglycerin when dry is a white, transparent, glassy, brittle, hygroscopic substance which forms a mass as it stands and absorbs water. It is soluble in hot water and, in solution, undergoes cleavage to glycerin and boric acid. Boroglycerin is not used as such, but instead, is converted to boroglycerin glycerite and used as an antimicrobial agent (Ref. 1). Boroglycerin glycerite is prepared by heating two parts of boric acid with three parts of glycerin, which is then dissolved in glycerin. Boroglycerin glycerite is a 50-percent solution of boroglycerin ($C_3H_3BO_3$) in glycerin (Ref. 2). Boroglycerin glycerite is a sweet, syrupy hygroscopic liquid. In aqueous solution, boroglycerin is more highly ionized than boric acid. As a consequence, its solutions are more irritating than those of boric acid. Boroglycerin glycerite was once, but is no longer, official in the "United States Pharmacopeia." Both boroglycerin glycerite and boroglycerin should be kept in tightly stoppered containers because they are hygroscopic.

(1) *Safety.* The Panel concludes that boroglycerin glycerite is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite is not safe because it is a derivative of boric acid and its action is due to the release of boric acid when boroglycerin glycerite is applied to wounds, burns, and other, lesions and on the mucous membranes of the mouth and throat. No data are available on the acute and chronic toxicity of boroglycerin or boroglycerin glycerite. Inasmuch as boroglycerin and boroglycerin glycerite are derivatives of boric acid and release boric acid during clinical use, it is the consensus of the Panel that their toxicity is similar to that of boric acid. (See part IV. paragraph B.2.a. above—Boric acid.) Glycerin, their other component, is relatively innocuous.

(2) *Effectiveness.* The Panel concludes that boroglycerin glycerite is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Boroglycerin glycerite contains 31 parts of boric acid and 96 parts glycerin. The anitimicrobial action of boroglycerin is due to the boric acid, which is slowly released when applied to burns. It is used externally, diluted with 10 parts of water. Since the active ingredient is boric acid, it can only be assumed that boroglycerin glycerite is not an effective antimicrobial agent. There are no controlled studies reported that establish it as an effective antimicrobial agent. Data on its effectiveness have not been supplied to the Panel in the submissions by manufacturers, and the Panel doubts that it is any more effective than boric acid. (See part IV. paragraph B.2.a. above—Boric acid.)

(3) *Evaluation.* The Panel concludes that boroglycerin glycerite be placed in Category II for both safety and effectiveness because it contains a boron derivative.

References

(1) "The Merck Index," 5th Ed., Merck and Co., Rahway, NJ, p. 91, 1940.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, pp. 602–603, 1948.

c. *Camphor.* The Panel concludes that camphor is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The general characteristics of camphor have been described elsewhere in this document. (See part III. paragraph B.2.b. above—Camphor.)

(1) *Safety.* The Panel concludes that comphor is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The safety of camphor has been descried elsewhere in this document. (See part III. paragraph B.2.b.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that camphor is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Applied locally, camphor is alleged to be weakly antiseptic, but no controlled studies have been submitted to support this contention. Camphor is a ketone and, as is common with other ketones, lacks antiseptic activity. Furthermore, the Panel has not evaluated any ketone that is a safe and effective antiseptic. Camphor is a rubefacient when rubbed on the skin. When not applied vigorously, however, it may produce a feeling of coolness. This sense of coolness is also felt when camphor is applied to the mucous membranes. Camphor has a mild local anesthetic action, and its application to the mucous membranes in appropriate concentrations may be followed by numbness.

Camphor is absorbed through both the mucous membranes and from the skin. Camphor is also used for its local anesthetic and antipruritic effect to relieve itching of the skin. It has been used in conjunction with phenol for local application to treat fungal infections. It is believed that camphor retards the release and absorption of phenol from a mixture, but instances of ulceration from single applications of the mixture have been reported. (Ref. 1). Camphor is dispensed as camphor oil liniment, camphor in soap liniment, and spirits of camphor, which is a 10-percent solution by weight and volume, of camphor in alcohol. This mixture of camphor and alcohol is locally irritating when applied topically. Camphor water is a saturated solution of camphor in purified water. It is sometimes used for its supposed astringent effect.

(3) *Evaluation.* The evaluation of camphor has been described elsewhere in this document. (See part III. paragraph B.2.b.(3) above—Evaluation.)

Reference

(1) Hubler, W. R., "Ulceration of the Feet Following Single Application of Camphor-Phenol Mixture," *Journal of the American Medical Association,* 123:990, 1943

d. *Cresol.* The Panel concludes that cresol is not safe and that there are insufficient data to classify cresol as an effective antimicrobial active ingredient for topical use on the mucous membrances of the mouth and throat.

Chemically, cresol is phenol with a methyl group on either the ortho, meta, or para positions of the benzene ring. Thus, cresol can exist in three isomeric forms. The pure forms of each are available but generally the mixture of the three is used for general and medical purposes. The cresols are obtaind by the fractional distillation of coal tar or petroleum. The mixture is predomintely metacresol which is the most toxic of the three. When the term "cresol" is used, generally the mixture is meant. Cresol is also known as tricresol, methylphenol, or cresylic acid. Cresol may contain traces of phenol.

Cresol consists of a colorless, pinkish or yellowish to brownish liquid which is highly refractory. Not less than 90 percent by volume distills betwen 195 and 205° C. It darkens with age and on exposure to light, as does phenol (Ref. 1). One milliliter dissolves in approximately 50 mL water, usually producing a cloudy solution. It is miscible with alcohol, glycerin, ether, and other organic solvents (Ref. 2). Like other phenols, it is acidic in reaction in aqueous solutions and forms salts in soluble alkaline metal hydroxides. Cresol is also dissolved in camphor to form a complex, camphor metacresol. This complex is similar to the camphor-phenol complex and releases cresol when it comes in contact with moisture (Ref. 3).

(1) *Safety.* The Panel concludes that cresol is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Because cresol is closely allied to phenol both chemically and parmacologically, it behaves as does phenol. Fatal cases of cresol poisoning have followed the ingestion of the drug or its use as a douche. It is readily and rapidly absorbed from the skin and mucous membrances. Cresol is somewhat less toxic than phenol due to the presence of the methyl group on the benzene ring. The symptoms of cresol poisoning and the treatment are similar to those for phenol. (See part III. paragraph B.1.g. above—Phenol.) When applied locally to the skin, cresol causes a burning sensation and an erythema, followed by numbness. It acts in the same manner as phenol and destroys tissue, cauterizing the area of application. After oral ingestion, severe burning sensations in the mouth and upper abdomen are felt. Dysphagia, vomiting, and diarrhea are common. White spots are seen on the mucous membranes after ingestion, indicating that the cresol has coagulated the cellular protein. It behaves exactly as does phenol in this regard (Ref. 4). Unconsciousness and circulatory collapse follow. If the patient survives, jaundice, oliguria, and uremia may develop due to injury to the liver and kidneys. Orally 8 g or more have been fatal to man. Cresol is a general protoplasmic poison. Data on absorption from the mucous membrances of the mouth and throat were not available, but the Panel surmises that it behaves like other phenols and is absorbed and passes into the systemic circulation and, therefore, has all the drawbacks of phenol.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of cresol as an OTC antimicrobial active ingredient for tipical use on the mucous membrances of the mouth and throat.

Cresol is an antimicrobial agent that surpasses phenol in germicidal and antiseptic activity. The substitution of an alkyl (methyl) radical or other side chain on the aromatic nucleus of phenol enhances its antimicrobial activity. Cresol is about three times more active than phenol as a germicide against many bacteria. It is four times more active against *Salmonella typhi* than phenol. The ortho isomer is the most actively germicidal of the three. Since cresol is sparingly soluble in water, it is generally employed in the form of a 50-percent solution dispersed with soap (saponated cresol solutions), which forms a clear solution with purified water, but a cloudy one with tap water because a precipitation of lime soaps occurs. Cresol is used largely for sterilization and sanitization and has limited use clinically as an antiseptic. Cresol has been used for sterilization of instruments in a 3- to 5-percent solution of the saponated mixture. One percent of saponated solution has been used for application to wounds. A 2-percent solution of cresol is suitable as a handwash. Cresol is used to disinfect excreta of patients with contagious diseases. Cresol is sometimes employed in a concentration of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions. A 0.2-percent aqueous solution has been used as a vaginal

douche, but is not recommended because adverse effects have resulted (Ref. 5).

Dilute solutions of cresol possess a topical anesthetic effect similar to that of phenol. It is, however, not used for this purpose.

Cresol must not be confused with creosol or creosote. Creosote is a mixture of phenols obtained from wood tar. The active ingredient in creosote is creosol, which is a methoxy cresol.

(3) *Evaluation.* The Panel has classified cresol as Category II because it is a phenol derivative which is caustic when applied topically and toxic when absorbed systemically. It produces local damage to tissues even in dilute solutions. Other agents are safer.

References

(1) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 294, 1960.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 810, 1957.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1102, 1975.

(4) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(5) OTC Volume 130006.

e. *Ferric chloride.* The Panel concludes that ferric chloride is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Ferric chloride ($FeCl_3$) occurs as hexagonal dark leaflets or plates. It is red by transmitted light and green by reflected light. Ferric chloride is very hygroscopic and melts and volatilizes at about 300° C. In air, it readily absorbs water to form the hexahydrate ($FeCl_3 \cdot 6H_2O$). Ferric chloride is readily soluble in water, alcohol, ether, and acetone. It has also been referred to as iron perchloride (Ref. 1).

The hexahydrate forms brownish-yellow or orange monoclinic crystals which are readily soluble in water, alcohol, acetone, and ether. Aqueous solutions are acid in reaction. The hexahydrate is described as an astringent and stypic (Ref. 1). Aqueous solutions of ferric chloride have been described in the "National Formulary." Each 100 mL of these solutions contained 37.2 to 42.7 g ferric chloride (Ref. 2). The solution was used as an astringent and styptic to arrest bleeding from cut surfaces and wounds. The tincture was also described in the "National Formulary." This was a yellowish-orange solution with an ethereal odor which is due to the formation of ethyl chloride and ethyl acetate by the action of the acid liberated from the iron chloride. It was also known as "iron perchloride tincture." The tincture consisted of 15 g ferric chloride in 100 mL of 58 to 64 percent ethyl alcohol. It was used orally but was highly irritating to the gastric mucosa.

Ferric chloride solutions and acid tinctures are incompatible with alcohols, iodides, tannin-containing solutions, and acadia mucilage.

(1) *Safety.* The Panel concludes that ferric chloride is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The oral LD_{50} in rats for iron chloride hexahydrate is 900 mg/kg. In rabbits, the intravenous LD_{50} is 7.2 mg/kg (Ref. 3).

No data were submitted to the Panel on acute and chronic toxicity studies in animals or on the teratogenicity and carcinogenicity of the compound. No data on acute or chronic toxicity in man were submitted. It is stated that the anhydrous form is an irritant (Ref. 1).

According to Gosselin et al. (Ref. 4), ferric chloride has a toxicity rating of 3 and the probable oral lethal dose in man is 0.5 to 5.0 g/kg. When given orally, both ferric and ferrous soluble compounds induce essentially the same type of toxic syndromes. The symptoms of poisoning due to derivatives of iron are severe gastritis or gastorenteritis with abdominal pain and prolonged vomiting beginning 10 to 60 minutes after ingestion. Vomitus may become bloody. Diarrhea is sometimes violent, and the feces are watery and later tarry. Dehydration becomes intense, and generalized itching may occur. Shock, pallor, cyanosis, coldness, rapid, weak, or imperceptible pulse, low blood pressure, and rapid and shallow respirations occur. Breathing is deep and rapid indicating the presence of a condition of metabolic acidosis. Drowsiness, hyporeflexia, dilated pupils, and coma may occur. Liver injury, consisting of hemorrhagic necrosis may occur, but it is usually reversible. Death from shock may occur within 4 to 5 hours. Sometimes, following apparent recovery, pneumonia with fever or secondary shock may develop and cause death 1 to 3 days later. Pyloric stenosis and mild hepatic cirrhosis may be encountered as sequelae among survivors, but recovery is usually complete without sequelae.

(2) *Effectiveness.* The Panel concludes that ferric chloride is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The tincture of iron chloride is an effective protein precipitant and was once used as a styptic. It also has been used as an astringent. The tincture has been mixed with equal parts of glycerin and water and applied to the throat by means of a swab to relieve pharyngitis. It has also been used as a gargle, but it is no longer recommended for this purpose because of its questionable effectiveness. In addition, the acidity of the solution is injurious to the teeth (Ref. 5). No data are available from controlled studies concerning the spectrum of its antimicrobial activity (Ref. 6). The antimicrobial effects tincture of iron chloride may manifest presumably are due to its protein-precipitating properties.

Ferric chloride preparations are not recommended for internal use.

(3) *Evaluation.* The Panel concludes that ferric chloride preparations are not safe for internal use. Furthermore, the Panel has no data on the antimicrobial effects of ferric chloride and concludes that preparations containing ferric chloride are not effective for topical use as antimicrobial active ingredients on the mucous membranes of the mouth or throat.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 523, 1976.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 571, 1955.

(3) Sector, W. S., editor, "Handbook of Toxicology: Volume I," W. B. Saunders Co., Philadelphia, pp. 140–141, 1956.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th E., Williams and Wilkins, Baltimore, section II, p. 97, and section III, p. 156, 1976.

(5) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co, Philadelphia, p. 1248, 1957.

(6) OTC Volume 130052.

f. *Maralein sodium.* The Panel concludes that meralein sodium (merodicein) is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Meralein soidum, better known as merodicein, is an organic mecurial antiseptic. Meralein sodium is (3'-6'-Dihydroxy-2', 7'-diiodospiro [3H-2, 1-benzoxanthiole-3, 9'-[9H]xanthen]-4-yl)-hydroxymercury 5,5-dioxide monsoidum salt; o-[6-hydroxy-5-)hydroxymercuri)-2, 7-diiodo-3-oxo-3H-xanthen-9-yl]-benzenesulfonic acid sodium salt; 2, 7-diido-4-hydroxymercuriresorcinsulfonphthalein monosodium salt (Ref. 1). Maralein

sodium is used as a topical antiseptic. It is supplied as a 1:5,000 aqueous solution for use in the mouth (Ref. 2). Meralein sodium consists of green scales that turn dark red. It is soluble in water. Aqueous solutions are slightly fluorescent.

(1) *Safety.* The Panel concludes that meralein sodium is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Gosselin et al. (Ref. 2) rate the toxicity of meralein sodium as 4 (very toxic). The probable lethal dose is 50 to 500 mg/kg. Gosselin et al. describe it as "A water-soluble germicide containing about 23 percent organically bound mercury." The minimal lethal dose parenterally in laboratory animals is 10 mg/kg. It is poorly absorbed from the gastrointestinal tract. Doses of 200 mg/kg have a laxative effect.

In an extensive study of the pharmacology and toxicology of meralein sodium, Macht and Cook (Ref. 3) showed that systemic poisioning was due to acute renal failure and found little effect on other organ systems. Gosselin et al. (Ref. 2) also showed that systemic poisoning leads to acute renal failure. When injected intravenously in a concentration of from 0.1 percent to 2.0 percent meralein sodium was carried by the circulation to the various organs where it conferred a pink color to the stomach, intestines, and other viscera (Ref. 2). Very little of the compound was deposited in the skin. Most of the meralein sodium was excreted via the intestinal tract, but small quantities were found in the urine and trace amounts in the bile. The saliva, even after pilocarpine was administered to promote the flow of saliva, contained no trace of the drug (Ref. 2).

(2) *Effectiveness.* The Panel concludes that meralein sodium is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Like many other mercurial antiseptics, meralein sodium is primarily bacteriostatic with bactericidal activity occurring slowly over a period of many hours. Bacteriostasis is readily nullified by the presence of many organic compounds, particularly those containing sulfhydryl radicals, such as thioglycollate, cysteine, and dimercaprol, and by glutathione, serum, and plasma (Ref. 4). This reversible bacteriostasis was clearly demonstrated by Engley (Ref. 5), who showed that virulent streptococci exposed to 0.2 percent meralein sodium for 10 minutes killed 10 out of 10 mice injected intraperitoneally. When the cells from the meralein sodium-treated cultures were transferred to dextrose broth, no growth occurred, but the addition of 0.1 thioglycollate or 10 percent serum to the broth enabled growth to occur in vitro just as it had in vivo.

One study indicates that the growth of *Staphylococcus aureus, Streptococcus pyogenes,* and *Pseudomonas aeruginosa* is merely inhibited when exposed to meralein sodium in a 1:5,000 concentration for 15 minutes, but that these bacteria are killed after 24 hours of exposure (Ref. 6). However, this is not of any clinical significance because it is unlikely that meralein sodium would remain in the mouth for more than 15 minutes and certainly not as long as 24 hours.

(3) *Evaluation.* The Panel concludes that the bacteriostatic effects of meralein sodium are transitory and insignificant. The bactericidal effects, likewise, are not significance since they occur slowly. Data on absorption from the mucous membranes are not supplied. Since the compound contains 23 percent mercury, it is not surprising that renal damage has been reported following its use. The Panel considers the compound toxic and not safe or effective for topical use in the mouth and throat.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 762, 1976.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 95, 1976.

(3) Macht, D. L., and H. M. Cook, "Pharmacology and Toxicology of Monohydroxy-mercuri-di-iodo-resorcinsulphonphthalein," *Journal of Pharmacology and Experimental Therapeutics,* 43:571–605, 1931.

(4) Lawrence, C. A., and S. S. Block, "Disinfection, Sterilization, and Preservation," Lea and Febiger, Philadelphia, pp. 362 and 366, 1968.

(5) Engley, F. B., "Evaluation of Mercurial Compounds as Antiseptics," *Annals New York Academy of Sciences,* 53:197–206, 1950.

(6) OTC Volume 130075.

g. *Nitromersol.* The Panel concludes that nitromersol is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Nitromersol is identified with the mercurial organic compounds that are used for antimicrobial purposes. Nitromersol is the anhydride of 4-nitro-3-hydroxymercuriocresol. It is prepared from orthotoluidine through a succession of steps of nitration, diazotization, and interaction with mercuric acetate resulting in a crystalline powder.

Nitromersol is considered an organic mercurial. The organic mecurials are compounds in which mercury is present in complex organic combination. As a group they are more bacteriostatic, less irritating, and less toxic than the inorganic mercurial salts. Nitromersol is composed of brownish to yellow granules or a brownish-yellow powder. It is odorless, insoluble in water, almost insoluble in alcohol and ether, but soluble in solutions of alkalis (Ref. 1).

(1) *Safety.* The Panel concludes that nitromersol is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Mercuric compounds can be absorbed and can be toxic to the renal tubules of the kidney. This action is less pronounced by organic mercurial compounds than by the inorganic mercurial compounds. Nitromersol has a slight protein-precipitating action. Like other mercurials, it has a tendency to sensitize the skin.

(2) *Effectiveness.* The Panel concludes that nitromersol is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The mechanism of action of mercurial compounds is not known exactly. It is believed that the mercuric ion inhibits the activity of enzymes containing sulfhydryl groups (SH) by combining reversibly with these groups. The inhibition of these enzymes by mercury, therefore, is reversible. When the metal is removed from the enzyme, the activity is restored. Bacteria and certain viruses inactivated by mercury compounds can be reactivated by removing the mercury with the use of thiols. Bacterial spores exposed to mercurials for many months resume multiplication when the inhibitor is removed. In the body fluids there are many sulfhydryl compounds such as glutathione, cysteine, and proteins which are capable of combining with mercury. Organisms inhibited by mercury therefore, can become reactivated when they are introduced into the body.

The mercurial antiseptics inhibit the sulfhydryl-containing enzymes of tissue cells of the host as well as those of the bacteria. Test objects such as embryonic tissue and other cells are readily injured by organic mercurial compounds. The therapeutic index of organic mercurial compounds is low. They are not considered ideal antiseptics and germicides.

The organic mercurial compounds are employed as substitutes for the more highly ionized mercury salts because they are less irritating and can be applied directly to the tissues. They have been widely used in

concentrations ranging from 1:100,000 to 1:1,000 to disinfect instruments and as antiseptics on cutaneous and mucosal surfaces. However, they are not efficient for disinfecting instruments, as is commonly believed. The organic mercurial compounds are primarily bacteriostatic and are relatively ineffective in killing spores. The organic mercurial antiseptics are available as various types of proprietary solutions, tinctures, jellies, ointments, and suppositories (Ref. 2).

Although several investigators reported sterilization of the skin with the use of an application of a 1:5,000 solution of nitromersol which is a first-aid solution, White and Hill (Ref. 3) found that this compound could not be relied upon to produce sterility when applied to the skin for 5 minutes. A 1:200 alcohol acetone solution is highly effective as an antiseptic. The solution called nitromersol tincture is used for preoperative preparation of the skin. Nitromersol is available in a 1:500 solution in water. Since nitromersol is not readily soluble in water, a mixture of sodium hydroxide and sodium carbonate are used to convert the nitromersol to a soluble compound. A 1:200 tincture in 10 percent acetone, 52.5 percent alcohol by volume, and distilled water, is available.

No data were submitted to the Panel establishing the effectiveness of nitromersol as an antimicrobial agent for the relief of sore throat and sore mouth.

(3) *Evaluation.* The Panel concludes that nitromersol is not safe because of its toxicity and sensitization potential. There are no data from controlled studies showing that nitromersol causes relief of symptoms due to sore throat or sore mouth resulting from antimicrobial activity.

References

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1096, 1975.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, p. 789, 1973.

(3) White, E. C., and J. H. Hill, "Inefficiency of Metaphen as a Skin Disinfectant," *Journal of the American Medical Association,* 95:27–28, 1930.

h. *Potassium chlorate.* The Panel concludes that potassium chlorate is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate occurs as colorless, lustrous crystals, as white granules, or as a white powder. It is odorless and has a cooling effect and a saline taste. One part potassium chlorate is soluble in 16.5 parts water. It is soluble in glycerin and slightly soluble in alcohol. Potassium cholorate should not come into contact with readily oxidizable substances because it forms explosive mixtures. Potassium chlorate explodes when mixed with sulfuric acid. It ignites and explodes if triturated with organic substances, such as sulfur, phosphorus, sulfite, hypophosphite salts, and other oxidizable substances. Potassium chlorate is incompatible with iodides and tartaric acid (Ref. 1).

(1) *Safety.* The Panel concludes that potassium chlorate is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate is not safe for internal use. Potassium chlorate poisoning was common when the drug enjoyed widespread use therapeutically. The poisoning resulted from overdose or from variations in susceptibilities and tolerance among different individuals. Ten grams are toxic; 15 to 30 g have been fatal. The mortality rate is about 70 percent when lethal doses are ingested. The symptoms may appear shortly after ingestion or may be delayed for 5 to 6 hours. Death has occurred as early as 6 hours and as late as 7 days after ingestion. Potassium chlorate is irritating to the gastrointestinal tract and the kidneys. Symptoms include nausea, vomiting, gastroenteritis, anemia, and hematuria. Gosselin and associates (Ref. 2) rate potassium chlorate as having a toxicity of 4 (very toxic). The chlorate ion is not metabolized readily and persists in the body for a long time. It may convert an indefinite amount of hemoglobin to methemoglobin. Asphyxia may result from the methemoglobinemia. The drug also causes hemolysis. The hemolyzed cells may produce emboli, and the released hemoglobin causes hematuria. It may also cause nephritis.

Chlorates are excreted mainly by the kidney into urine. About 90 percent of a dose is eliminated unchanged. The urinary excretion of a dose begin promptly and is complete within 24 to 48 hours. Chlorates are also partly excreted by the salivary glands into the mouth. When chlorates were first introduced into therapeutics, they were considered to be innocuous and safe. This has not proved to be the case as time has passed.

(2) *Effectiveness.* The Panel concludes that potassium chlorate is not effective as an antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium chlorate solutions, in concentrations ranging from 2 to 4 percent, have been used as mouthwashes and gargles for infections of the mouth and throat, even though they are potentially toxic and of questionable value (Ref. 3). The saturated solution has been used as a mouthwash to treat stomatitis, particularly when ulcerative lesions have been present. Potassium chlorate was introduced because it was believed that it would act as an oxidizing agent and exert antiseptic action by releasing oxygen. This does not appear to be its mode of action. It is eliminated largely unchanged and is not altered in the body.

Potassium chlorate is of doubtful effectiveness since there are no data from controlled studies to support the claim that it relieves symptoms of sore throat or sore mouth or both when used as an antimicrobial agent. It has been used in lozenge form. This imparts a "clean" saline taste of potassium chlorate to the mouth, which supplants the normally existing "unflavored taste." Potassium chlorate also is used in tablet form. The tablets consist of 0.25 g of the salt and are placed on or beneath the tongue two to five times daily where they slowly dissolve and exert their therapeutic affect. After using the tablets for several days, the saline taste persists due to the salt that is excreted into the mouth from the salivary and other exocrine glands (Ref. 4).

Chlorates do not manifest antimicrobial activity in cultures. How it came to be adopted as an antimicrobial agent has puzzled physicians.

Potassium chlorate has been combined with ferric chloride and balsam of tolu for use as a demulcent, and with glycerite and boroglycerin (Ref. 5).

(3) *Evaluation.* It is the consensus of the Panel that potassium chlorate is neither safe nor effective as an OTC active antimicrobial agent for topical use in the mouth and throat and that it be placed in Category II.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 990, 1976.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 76, 1976.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 891, 1977.

(4) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 794–795, 1947.

(5) OTC Volume 130052.

i. *Sodium dichromate.* The Panel concludes that sodium dichromate (also bichromate) is not safe and that there are insufficient data to classify its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium dichromate is a derivative of chromium. Elemental chromium is used in medicine in the form of sodium or potassium dichromate. Sodium chromate is the sodium salt of chromic acid. The empiric formula for sodium chromate is $Na_2CrO_4 \cdot 4H_2O$. Sodium chromate loses its water of hydration to form an anhydrous salt. It also forms a crystalline hydrate with 10 molecules of water. The anhydrous form is a yellow powder. The hydrated form is soluble, about 1 part in 1 part of water. The aqueous solution is alkaline. Sodium chromate is also slightly soluble in alcohol. It is used to prevent rusting of iron.

The potassium salt (K_2CrO_4) has similar properties as the sodium salt. Sodium dichromate ($Na_2Cr_2O_7$) and potassium dichromate ($K_2Cr_2O_7$) are prepared by reacting sodium or potassium chromate with sulfuric acid (Refs. 1 and 2). Sodium chromate forms a dihydrate which consists of copper-colored, bright orange, or yellowish crystals. Its solutions are acidic. The pH of a 1-percent solution is 4, and the pH of a 10-percent solution is 3.5. The chromates are combined with sulfuric acid for cleaning glassware in laboratories (Ref. 1).

(1) *Safety.* The Panel concludes that sodium dichromate is not safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Chromium derivatives are used in medicine in the form of chromic acid or in the form of either the sodium or potassium bichromates. They are also used in the disodium and dipotassium forms. Derivatives of chromium are active oxidizing agents. In addition, they are poisons when ingested since they form chromous oxide, CrO, which is the anhydride of chromic acid.

Gosselin et al. (Ref. 3) give sodium dichromate a toxicity rating of 4 to 5 with a mean lethal dose probably of about 10 g. It is highly corrosive to skin and mucous membranes. If ingested, violent gastroenteritis, peripheral vascular collapse, vertigo, muscle cramps, coma, hemorrhagic diathesis, fever, liver damage, and acute renal failure occur. Methemoglobinemia occurs probably due to sodium dichromate's oxidizing properties. Sodium dichromate also causes intravascular hemolysis, as is the case with chlorate salts. When dichromates are ingested orally they are reduced to chromous oxide and partly deposited as such in various organs. The remainder is excreted in the urine. Chronic nephritis is produced experimentally by intravenous injection of chromates. The toxic effects of chromium derivatives are not only due to the fact that the resulting oxide is a poison when ingested, but also because they act sumultaneously as oxidizing agents while they are undergoing the chemical changes to the oxide in the body (Ref. 4). Derivatives of chromium used in various manufacturing processes are considered to be industrial hazards since they are poisons. Extreme precautions are taken to avoid their ingestion, inhalation of powders of the salts, or cutaneous absorption when they are used for industrial purposes (Ref. 2).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of sodium dichromate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium dichromate and other derivatives of chromium have been used as antimicrobial agents because of their oxidizing effects. They have no use as therapeutic agents because of their extreme toxicity. They were formerly used as astringents for the treatment of excessive sweating of the skin and as caustic agents to remove cutaneous lesions, neoplasms, etc. They were also used internally to treat gastric ulcers. Aqueous solutions of 5 percent sodium dichromate have been used on the skin without irritation; however, 10 percent solutions are caustic. Two to 3 percent aqueous solutions have been used as astringents and antimicrobial agents (Ref. 5). The pharmacologic actions of the sodium derivative are similar to those of the potassium derivative (Refs. 2 and 4).

(3) *Evaluation.* The Panel concludes that sodium dichromate is not safe for topical use on the mucous membranes of the mouth and throat because it is absorbed, and the systemic toxicity that results is characterized by nephritis and other organic syndromes.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1112, 1976.

(2) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 148, 1947.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 76, 1976.

(4) Sollmann, T., " A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 937, 1948.

(5) OTC Volume 130041.

j. *Tincture of myrrh.* The Panel concludes that tincture of myrrh is not safe and not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Myrrh belongs to the class of substances known as balsams or aromatic resins. Myrrh is categorized as an oleoresin. The oleoresins, in general, are oily substances containing largely benzoic and cinnamic acids and other constituents. They are considered to be mildly irritant and to stimulate the repair of tissues because of the substances contained in their oily components (Ref. 1). The resins furnish local protection and allegedly allay inflammation. Balsams and oleoresins are applied in cases of chronic inflammation of the mucous membranes and of the skin to promote healing of ulcers and wounds (Ref. 2).

Myrrh, also known as myrrha, is a gum resin obtained from camphora species (Ref. 3). It was used by the ancients as incense in religious ceremonies and by the Egyptians for embalming in combination with spices and other substances. Myrrh was formerly listed in the "United States Pharmecopeia." The botanical source of myrrh is *Commiphora molmol.* It is also obtained from Commiphora abyssinica and other species of camphora. The name "myrrh" is possibly derived from the Arabic and Hebrew word "mur" meaning bitter, The drug was also called "mulmul" and "ogo" by the natives of Somaliland and "herrabol" by the Indian traders. Myrrh is collected in Somaliland and Arabia by making incisions into the bark of the stems of trees. A gum-oleoresin film forms and reservoirs of the fluid collect beneath this film. These are punctured, and the myrrh is allowed to exude. The myrrh then hardens and is scraped off the bark. Most of the drug used in the United States is gathered from Somaliland and Arabia. In 1952, 19,040 pounds of myrrh were imported from British Somaliland.

Myrrh yields not less than 30 percent of alcohol-soluble extractives and not more than 5 percent of acid-insoluble ash. It contains from 3 to 8 percent of an oxygenated volatile oil, a bitter principle, about 50 to 60 percent of gum, and 25 to 40 percent of resin. The resin contains three isomeric forms of commiphoric acid, an ester of commiphorinic acid, and two isometric

forms of myrrolic acid. The volatile oil, which has been called myrrhol or myrrhenol, contains eugenol, meta-cresol, cuminaldehyde, cinnamaldehyde, pinene, dipentene, a sesquiterpene, and esters of formic, acetic, and myrrholic acids. The gum, with properties similar to arabin and acacia, yields pentosans, galactans, xylans, and arabans upon hydrolysis. The gum also contains an oxidizing enzyme (Refs. 4, 5, and 6). Myrrh has been used both in its natural form and as a tincture. The preparation reviewed by this Panel is the tincture.

(1) *Safety.* The Panel concludes that tincture of myrrh is not safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The ancient Greek physicians used myrrh locally as well as internally. Since it is an oleoresin, it has the properties of other oleoresins in being a mild irritant (Ref. 7). Because of these irritant properties, myrrh has been used as a component of laxative preparations. It has also been used in the form of the tincture which contains an alcohol-soluble extract of 20 percent of the drug. Internally, myrrh was once used as a carminative (Ref. 2). Myrrh and tincture of myrrh were official in "United States Pharmacopeia, XIII." They were not admitted to the "United States Pharmacopeia, XIV." They were admitted to the "National Formulary IX." They maintained official status until 1965 when both were dropped and not admitted to either compendium.

Animal toxicity studies, from which the Panel could make judgment, were not available.

(2) *Effectiveness.* The Panel concludes that tincture of myrrh is not effective as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

The comments concerning tincture of myrrh's therapeutic effectiveness are merely anecdotal, and there are no controlled studies to substantiate that it is an effective active ingredient. Tincture of myrrh has been applied loclly to "stimulate" spongy gums, to treat aphthous stomatitis, and ulcerations of the throat (Ref. 6). In its diluted form, tincture of myrrh has been employed in mouth rinses, for treating stomatitis, and in other lesions of the oral cavity (Ref. 2). The dosage range of myrrh is 0.3 to 1.2 g. The dosage range of tincture of myrrh is 1 to 2 mL. It has been used as a component of aloes and myrrh pills and compound pills of rhubarb (Ref. 8). Both OTC preparations currently on the market contain myrrh as a component of a combination product of several ingredients.

The Panel concludes that, since myrrh is a mixture of many substances and that since it has fallen into disuse in general medical practice, it has no place in modern therapeutics. Obviously, myrrh has been supplanted by other medicines whose pharmacologic action has been established.

(3) *Evaluation.* The Panel concludes that myrrh is a mixture of many substances, the active principle of which has not been identified. There is a paucity of data on the pharmacologic activity and safety of myrrh, and it cannot be adequately evaluated. Myrrh has fallen into disuse, and the Panel concludes that tincture of myrrh should be placed in Category II.

References

(1) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 49, 1965.

(2) Sollman, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, p. 147, 1948.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 822, 1976.

(4) Lyman, R. A., "Textbook of Pharmaceutical Compounding and Dispensing," 2d Ed., J. B. Lippincott, Philadelphia, p. 283, 1955.

(5) Darlington, R. C., "Topical Oral Antiseptics, Mouthwashes and Throat Remedies," *in* "Handbook of Non-Prescription Drugs," 4th Ed., edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, pp. 123–134, 1973.

(6) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott, Philadelphia, pp. 875–877, 1955.

(7) Thienes, C. H., and T. J. Haley, "Clincial Toxicology," 4th Ed., Lea and Febiger, Philadelphia, pp. 61–68, 1964.

(8) "The National Formulary," 6th Ed., American Pharmaceutical Association, Washington, pp. 396 and 399–400, 1935.

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing antimicrobial agent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Healing aid."

(2) "Relieves dryness."

(3) "For relief of pain and discomfort due to minor sore throat."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "For fast temporary relief of minor throat and mouth soreness."

(2) "Fast healing aid,"

(3) "Kills germs in minutes."

(4) "Kills germs by the millions on contact."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Multiaction germ killer."

(2) "Kills germs by the millions on contact."

(3) "General antiseptic application as an aid to wound healing."

(4) "Soothing cleansing antiseptic for mouth and throat."

(5) Adding such terms as "plus" etc.

d. *Statements or phrases that are vague in their meaning and that cannot be readily understood or are misleading.* (1) "Healing and for minor oral inflammations."

(2) "First aid for throat irritations."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion the diagnosis of which must be made by a physician.* (1) "As an aid to professional care of minor inflammation of the mouth and throat."

(2) "Healing aid for minor oral inflammations."

(3) "For temporary relief of minor sore throat due to common cold."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Prevents infection" (of the mouth and throat).

(2) "Helps provide breath protection."

(3) "As an adjunct for prophylaxis of Vincent's infection."

(4) "Healing and deodorizing solution."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Inhibits odor forming bacteria."

(2) "Deodorizing mouth wash and gargle."
(3) "Oral antiseptic cleanser."
(4) "For oral hygiene."
(5) "For general oral hygiene, bad breath."
(6) "Management of mouth odors, bad breath,"
(7) "An aid to daily care of the mouth,"
(8) "Helps provide soothing temporary relief of dryness and minor irritations of the mouth."
(9) "For causing the mouth to feel clean."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or type of formulation containing the ingredient(s) instead of designating the symptoms which the product is intended to relieve.* (1) "Antiseptic, oral antiseptic."
(2) "Antimicrobial."
(3) "Antiseptic drops."
(4) "An effective antiseptic when undiluted."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

Benzalkonium chloride
Benzethonium chloride
Benzoic acid
Carbamide peroxide in anhydrous glycerin
Cetalkonium chloride
Cetylpyridinium chloride
Clorophyll
Dequalinium chloride
Domiphen bromide
Ethyl alcohol
Eucalyptol
Gentian violet
Hydrogen peroxide
Iodine
Menthol
Methyl salicylate
Oxyquinoline sulfate (8-hydroxyquinoline)
Phenol
Phenolate sodium
Povidone-iodine
Secondary amyltricresols
Sodium caprylate
Thymol
Thymol iodide
Tolu balsam

a. *Benzalkonium chloride.* The Panel concludes that benzalkonium chloride is safe, but that there are insufficient data to classify its effectiveness as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzalkonium chloride is a mixture of alkyldimethylbenzylammonium chlorides with the empiric formula $[C_6H_5CH_2N(CH_3)_2R]$ Cl. R represents alkyl groups of varying lengths beginning with n-C_8H_{17} to n-$C_{18}H_{37}$. The mixture is so composed that the average molecular weight of the final product is 360 daltons. It is emphasized that benzalkonium is not a single entity compound, but a mixture of very closely allied derivatives (Ref. 1).

Domagk, in 1935, called attention to the antiseptic and detergent properties of certain quaternary ammonium compounds and noted in particular that benzalkonium chloride was most effective (Ref. 2).

Benzalkonium chloride possesses the structural requirements for a quaternary ammonium compound having high germicidal activity, namely, the presence of a long alkyl hydrocarbon chain, one short aromatic-substituted alkyl group (benzyl), and two shorter alkyl groups (methyl). (See part IV. paragraph A.8.a above—The quaternary ammonium compounds.) The long alkyl hydrocarbon chain is obtained from the fatty acids of coconut oil; because the composition of coconut oil is reasonably constant, a uniform composition of the product is assured.

Benzalkonium chloride is usually available as a white to yellowish-white powder, but it may exist as a thick gel or as dried lumps of gelatinous pieces. It is very soluble in both water and alcohol. Aqueous solutions foam copiously when agitated.

Benzalkonium chloride is a cationic detergent, i.e., one whose antiseptic and detergent properties reside in the cation and as such is incompatible with any anionic detergent, such as soap, in which the detergent effect resides in the anion. Soap should be completely removed from tissues to which benzalkonium chloride solution is to be applied (Ref.3).

(1) *Safety.* The Panel concludes that benzalkonium chloride is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Effective concentrations of benzalkonium chloride are relatively nonirritating to the skin. They are said to have an emollient action. A 1:1,000 solution was given orally to guinea pigs as their only source of fluid for months without apparent harmful effects. Daily intraperitoneal injections of as much as 6 mL of the 1:1,000 solution for several months also showed no apparent reaction. Single doses of 1.2 mL/kg of body weight of a 10-percent solution produced little or no effect in rabbits when injected subcutaneously or intraperitoneally. When the dose was increased to 1.5 mL/kg, death occurred within 24 hours due to local destruction of tissue rather than systemic toxicity.

In reporting the death of a woman following artificial abortion with benzalkonium chloride, Arnold and Krefft (Ref. 4) stated that in animals the substance is extremely toxic following intraperitoneal or intravenous injection. It produced, according to these investigators, a curare-like effect with paralysis of neuromuscular junctions of all striated muscles, which was similar to the effect observed in the woman. Extreme caution is advised by Arnold and Krefft in using benzalkonium chloride for washing body cavities, especially if the solution is to be kept in place for a long time. These manifestations of toxicity are consistent with the pharmacologic behavior of many quaternary nitrogenous compounds. They manifest ganglionic blocking effects and a curare-like action.

There are little data of any significance obtained from controlled studies on the absorption of benzalkonium chloride from the mucous membranes. Quaternary nitrogenous compounds are highly ionized and, therefore, do not penetrate lipid barriers of the cell membrane since they are not lipophilic. They are not readily metabolized by the microsomal reticulum of the liver and are excreted almost entirely unchanged through the kidney. The Panel cautions, however, that the presence of a lipophilic group could modify absorption and possibly enhance it.

The Panel finds no data from controlled studies on the cumulative effects resulting from absorption from the mucous membranes of benzalkonium chloride when used on a day-to-day basis in mouthwashes or rinses for years. There are no data on the tumorigenic, mutagenic, or teratogenic potential of the agent when used under similar circumstances or during pregnancy.

The human fatal dose of quaternary nitrogenous cationic agents has not been established; it is believed to be between 1 and 3 g. Concentrated solutions are primary skin irritants, but percutaneous absorption is not considered to be significant. Although these agents can be haptenogenic and cause systemic and local allergic responses, the incidence of sensitization is low. Benzalkonium chloride is less injurious to human leukocytes than are the mercurial antiseptics (Ref. 5).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzalkonium chloride

as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzalkonium chloride is a powerful and rapidly acting germicide for many pathogenic nonsporulating bacteria and fungi. Solutions of the substance have a low surface tension (37.4 dyn/cm for a 1:1,000 solution at 25.3° C) and possess detergent, keratolytic, and emulsifying properties. All of these qualities favor wetting and penetration into surfaces to which solutions of benzalkonium chloride are applied. In vitro tests have demonstrated that *Streptococcus haemolyticus* is killed within 10 minutes (but not in 5 minutes) by a 1:40,000 solution at 20° C, and by a 1:95,000 solution at 37° C; for *Staphylococcus aureus* the corresponding letal dilutions are 1:20,000 and 1:35,000; for *Eberthella typhosa* they are 1:20,000 and 1:70,000; and for *Escherichia coli,* 1:12,000 and 1:40,000. In the presence of serum the effective concentrations were approximately 10 times greater (Refs. 6 through 9).

On the skin, under the usual conditions of use, the disinfectant action of benzalkonium chloride is not as great as has been generally supposed, principally because residual soap on the skin inactivates the detergent (Ref. 10). (See part IV. paragraph A.8. above—Quaternary nitrogenous cationic antimicrobial agents.) Thorough rinsing to the area to which benzalkonium chloride is to be applied, with water, will materially enhance its effectiveness. Price (Ref. 10) has demonstrated that the "tincture" of benzalkonium chloride, in which the solvent is composed of 50 percent ethyl alcohol, 10 percent acetone, and 40 percent water, is not only a more effective skin disinfectant than an aqueous solution of equal concentration, but also is less affected by soap than is the aqueous solution. The strongest disinfectant action, according to Price (Ref. 10), is produced by a 1-percent iodine solution in 70 percent alcohol; the next strongest is 70 percent alcohol; the next strongest is 70 percent (by weight) alcohol by itself; third is the tincture of benzalkonium chloride.

Miller and associates (Ref. 11) reported that certain cationic antiseptics of the type of benzalkonium chloride deposit an invisible film on the skin which is difficult to remove. This film may be sterile on the outside, but underneath it the skin may hold viable bacteria; it is readily removed by alcohol or by application of an anionic detergent, such as soap.

Adsorption of benzalkonium chloride by cotton guaze sponges placed in a solution of the compound, thereby reducing the germicidal effectiveness of the solution, may have been responsible for the viability of an organism isolated from a solution that caused infection when used for skin disinfection in a hospital (Ref. 12).

Aqueous or alcohol-acetone-water solutions of benzalkonium chloride may be employed on the skin to reduce the microbial population. Where the skin has been washed with soap and water, careful rinsing with water, then with 70 percent alcohol, is to be followed by application of the "tincture" of benzalkonium chloride. Aqueous solutions of benzalkonium chloride are employed on areas where soap is not ordinarily used or where alcohol would produce irritation.

Concentrations of benzalkonium chloride recommended for topical uses are as follows: preoperative disinfection of skin, 1:750 tincture or solution; minor wounds and lacerations, 1:750 tincture; deep infected wounds, 1:20,000 to 1:3,000; denuded skin and mucous membranes, 1:10,000 to 1:5,000; vaginal douche and irrigation, 1:5,000 to 1:2,000; bladder and urethral irrigation, 1:20,000 to 1:5,000; bladder retention lavage, 1:40,000 to 1:20,000 eye irrigation, 1:10,000 to 1:5,000; ear and antrum irrigation, 1:10,000 to 1:1,000; preservation of ophthalmic solutions, 1:7,500 to 1:5,000; storage of catheters and other adsorbent materials, 1:500; storage of thermometers, and metallic instruments, 1:750 (aqueous); general hospital disinfection, 1:25,000.

Benzalkonium chloride, in 1:5,000 concentration, was found by Lawrence (Ref. 13) to be the most effective of several agents evaluated for antimicrobial activity in ophthalmic solutions; at this concentration destruction of test organisms was achieved in 30 minutes.

Benzalkonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel believes that benzalkonium chloride is of limited clinical usefulness as a topical antimicrobial agent for the temporary relief of occasional symptoms of sore mouth or throat because its antimicrobial spectrum is limited, especially by the uncertainty imposed by environmental factors such as the presence of proteins, neutralizing anions, and organic materials in the mouth. Furthermore, the evidence is overwhelming that the topical application of antimicrobial agents to infected and inflamed areas is of doubtful therapeutic value, is not necessarily curative, may not ameliorate a disease process, and may even aggravate an inflammatory state. Certain antimicrobial agents are of value for select infections for which the agent is specifically microbicidal. Such specific conditions can only be diagnosed by a physician or dentist and are not amenable to self-diagnosis or treatment by a consumer, such as would be appropriate for using OTC products.

The Panel does not recommend mouthwashes, rinses, sprays, or lozenges containing benzalkonium chloride as an antimicrobial agent for use as deodorants, cleansing, prophylaxis, or for oral health care on a daily basis or for protracted periods of time, particularly in situations that are devoid of symptoms. (See part IV. paragraph A.2. above—Antimicrobial agents for use in the oral cavity.)

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of benzalkonium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.01- to 0.02-percent concentration of benzalkonium chloride in the form of a rinse, mouthwash, gargle, spray, or by swabbing digitally or using a nonadsorbent applicator, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1088, 1975.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 182, 1973.

(3) Windholz, M., editor, "The Merck Index," Merck and Co., Rahway, NJ, p. 137, 1976.

(4) Arnold, W., and S. Krefft, "Untersuchungen zur Toxicitat des Zephirols," *Deutsche Zeitschrift fur gerichtliche Medizin,* 41:297–310, 1952.

(5) Herrell, W. E., and D. Heilman, "Tissue Culture Studies on Cytotoxicity of Bactericidal Agents: III. Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin; Compared with Other Germicides," *American Journal of Medical Science,* 206:221–226, 1943.

(6) Dunn, C. G., "A Mixture of High Molecular Alkyl-dimethyl-benzyl-ammonium Chlorides as an Antiseptic," *Proceedings of the Society for Experimental Biology and Medicine,* 35:427–429, 1936.

(7) Dunn, C. G., "Fungicidal Properties of Alkyl-Dimethyl-Benzyl Ammonium Chlorides," *Proceedings of the Society for Experimental Biology and Medicine,* 37:661–663, 1938.

(8) Dunn, C. G., "A Comparative Study of Some Antiseptics and Germicides with Special Reference to Alkyl-Dimethyl-Benzyl Ammonium Chloride," *American Journal of Surgery,* 41:268–271, 1938.

(9) Hoyt, A., R. T. Fisk, and G. Burde, "The Antibacterial Action of Certain Disinfectants," *Surgery, 12:786–790, 1943.*

(10) Price, P. B., "Benzalkinium Chloride (Zephiran Chloride) as a Skin Disinfectant," *Archives of Surgery, 61:23–33, 1950.*

(11) Miller, B. F., et al., "Formation of Invisible, Non-perceptible Films on Hands by Cationic Soaps," *Proceedings of the Society for Experimental Biology and Medicine,* 54:174–176, 1943.

(12) Malizia, W. F., E. J. Gangarosa, and A. F. Goley, "Benzalkonium Chloride as a Source of Infection," *New England Journal of Medicine,* 263:800–802, 1960.

(13) Lawrence, C. A., "An Evaluation of Chemical Preservatives for Ophthalmic Solutions," *Journal of the American Pharmaceutical Association (Scientific Edition),* 44:457–464, 1955.

b. *Benzethonium chloride.* The Panel concludes that that there are insufficient data available to permit final classification of the safety and effectiveness of benzethonium chloride as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium is identified with the group of surface active agents that possess antimicrobial activity belonging to the family of cations derived from pentavalent nitrogen. Four of the five bonds are covalent, and one is ionic. Benzethonium is a base derived by substituting the four hydrogen atoms of the ammonium ion with organic radicals. When dissolved in water, a base forms that is ionized into a quaternary ammonium ion and a hydroxyl ion. The base forms salts with organic and mneral acids, usually hydrochloric, in the same manner as does ammonium hydroxide. Benzethonium chloride is benzyldimethyl[2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxyl]ethyl]ammonium chloride and contains, on a dry basis, not less than 97 percent of $C_{27}H_{42}ClNO_2$. In an aqueous solution it ionizes and yields a substituted ammonium cation and a chloride ion. The biologically active ion is the substituted ammonium cation. It is similar in chemical structure to the other quaternary nitrogenous bases that possess antimicrobial activity. One of the substituents on the nitrogen atom is a high molecular weight aliphatic chain that confers lipophilic properties to the compound.

Benzethonium chloride is a white powder composed of colorless crystals. It melts at approximately 162° C. It is soluble in water, alcohol, and in chloroform. The monohydrate consists of thin hexagonal plates.

(1) *Safety.* The Panel concludes that there are insufficient data to permit final classification of the safety of benzethonium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium chloride has a low order of toxicity in animals and man and is probably safe in low dosages when used occasionally for short-term therapy. Herrell and Heilman (Ref. 1) tested the toxicity of benzethonium chloride to human leukocytes and found it less injurious than mercurial antimicrobial agents. The LD_{50} in rats orally is 450 mg/kg. Effective concentrations are relatively nonirritating. Ordinarily, salts of quaternary nitrogenous compounds are not lipophilic, are not ionized, and are poorly absorbed through the mucous membranes. The introduction of a highly lipophilic radical into the structure presumably increases the lipid solubility, and penetration through epithelial barriers of cell membranes is enhanced. Systemic absorption therefore is increased, and it is possible for toxic doses to be absorbed from the mucous membranes. Toxic doses can be ingested accidentally, resulting in vomiting, collapse, coma, and convulsions. Quaternary nitrogenous bases ordinarily acting systemically are ganglionic-blocking agents and have a curareform action. Toxic manifestations cause depression of the autonomic nervous system effects and also cause muscle weakness due to a blockade at the myoneural junction. Caution should be exercised when solutions are used for instillation into or irrigating hollow cavities, especially if the solution remains in place for a long time. There is a possibility of absorption of toxic quantities. Adequate data on absorption and attainment of toxic blood levels and the metabolic fate of the "quats" are not available. Data on cumulative effects from continued use on a day-to-day basis over the span of years or a lifetime as would be the case when they are incorporated in mouthwashes are not available. The human fatal dose for quaternary nitrogenous cationic agents has not been established but is believed to be between 1 to 3 g. Although concentrated aqueous solutions are irritant to the skin, percutaneous absorption does not appear to be significant. Benzethonium chloride is absorbed through the mucous membranes of the mouth and throat, but quantitative data from controlled studies are not available. As is the case with other drugs, these agents can act as haptens and cause systemic and local allergic responses. However, the incidence of sensitization is low. No data are available on the mutagenic, tumorigenic, or teratogenic effects of benzethonium chloride when used in mouth rinses or gargles for long-term use on a daily basis for oral health care. There are no data on its effect on the fetus during pregnancy when used daily as a mouthwash.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzethonium chloride as an OTC antimicrobial agent for use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzethonium chloride was found to be the most active of a series of chemically allied quaternary ammonium antimicrobial agents studied by Rawlins and associates (Ref. 2). Since that time the pyridinium and quinaldinium compounds have been introduced and this statement, though still correct for the substituted ammonium compounds, is not necessarily applicable to these newer drugs.

Benzethonium chloride was tested by the FDA method on 8 different species of bacteria. These were killed within 5 minutes when concentrations ranging from 1:12,000 to 1:80,000 were used at 20° C in vitro. It was also noted that benzethonium chloride was strongly fungicidal. A 1:1,000 solution killed actinomyces, trichophyton, monilia, and other fungi. Benzethonium chloride has come into rather wide usage as a general germicide and antiseptic for reducing the microbial population of the skin and as an antiseptic for minor

wounds. The most commonly used preparations are 1:1,000 aqueous solutions and a 1:5,000 tincture (alcohol-acetone solution).

The activity of benzethonium chloride, in common with other quaternary nitrogenous antimicrobial agents and in contrast to other types of antimicrobial agents, is greatly lessened or completely nullified by numerous substances. These substances include anionic agents, such as soaps, and a variety of organic substances, such as proteins including blood, pus, and chemicals that act on adsorbents such as cotton. Miller and associates (Ref. 3) observed that this type of antiseptic forms a thin, relatively tough film on skin. The film may be sterile on the exterior but may be holding viable bacteria beneath. One alleged advantage in using benzethonium chloride is that its germicidal activity increases as pH increases. At pH 10, it is several times more active against *Eubacterium typhosa* and *Staphylococcus aureus* than at pH 4.

In a study of the effectiveness of quaternary ammonium compounds on molluscacides, a concentration of 10 parts per million of benzethonium chloride (hyamine 1622) killed all australorbis species of snails (Ref. 4). This fact is of importance from the standpoint of sanitation since these snails serve as the intermediate host of schistosoma. The potential importance of this property is obvious.

A 1:1,000 aqueous solution is available as an antimicrobial agent for use on the skin and mucous membranes. Benzethonium has been recommended as an antiseptic in preoperative and postoperative care of wounds and infected areas and also for application to accessible mucous membranes such as those of the eye, mouth, throat, and the gastrointestinal and genitourinary tracts. Tincture of benzethonium chloride is a 1:500 solution of the ingredient in alcohol and acetone; it is recommended principally for preparation of skin preoperatively and for antepartum preparation of obstetrical patients. A 1:5,000 ophthalmic solution, also containing 2 percent of boric acid, is supplied for use in ocular conditions where an antiseptic is indicated.

The germicidal and detergent properties of benzethonium chloride are utilized for sanitation purposes. It is available in crystalline form for this purpose. Benzethonium chloride is recommended for sanitizing eating and cooking utensils in restaurants, for similar use in dairies, for control of obnoxious odors in public rest rooms, for disinfectant use in laundering operations, for various veterinary germicidal uses, and for controlling algae growth in swimming pools. It is essential, of course, that it be used in proper concentrations for each of these purposes.

Benzethonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that, even though benzethonium chloride is effective as an antimicrobial agent in many situations, there are no data from controlled studies that establish it as an effective topical antimicrobial agent for the relief of symptoms of sore mouth or throat or both. Its antimicrobial spectrum is limited and made more so by the uncertainty imposed by environmental factors such as the presence of neutralizing anions, proteins, and organic materials found in the mouth and throat. Furthermore, there is no convincing evidence that the topical application of antimicrobial agents to infected and inflamed areas is of therapeutic benefit. In fact there is evidence that direct, topical application of antimicrobial agents may even aggravate an inflammatory state. (See part IV. paragraph A. above—General Discussion.) The Panel notes that there is no substantial evidence to establish the rationale for using benzethonium chloride on a continuing day-to-day basis as an antimicrobial agent in mouthwashes or rinses when no symptoms of any disease processes are present and in the absence of some obvious prophylactic or therapeutic need.

The Panel concludes that there are insufficient data to justify the use of benzethonium chloride in various mouthwashes, rinses, sprays, or lozenges and other oral health care use (Refs. 5 and 6). (See part IV. paragraph A. above—General Discussion.)

The Panel further concludes that there are insufficient data from controlled studies to establish the effectiveness of benzethonium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat when used within the proposed dosage limit set forth below.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a0.02- to 0.1-percent concentration of benzethonium chloride in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1 above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredient. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Herrell, W. E., and D. Heilman, "Tissue Culture Studies on Cytotoxicity of Bactericidal Agents: III. Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin; Compared with Other Germicides," *American Journal of Medical Science,* 206:221–226, 1943.

(2) Rawlins, A. L., L. A. Sweet, and D. A. Joslyn, "Relationship of Chemical Structure to Germicidal Activity of a Series of Quaternary Ammonium Salts," *Journal of the American Pharmaceutical Association (Scientific Edition),* 32:11–16, 1943.

(3) Miller, B. F., et al., "Formation of Invisible, Non-perceptible Films on Hands by Cationic Soaps," *Proceedings of the Society for Experimental Biology and Medicine,* 54:174–176, 1943.

(4) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 186, 1973.

(5) OTC Volume 130102.

(6) OTC Volume 130115.

c. *Benzoic acid.* The Panel concludes that benzoic acid is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid is the simplest carboxy acid of the aromatic series, being a benzene ring with a carboxyl group. It is also known as phenylcarboxylic acid, phenylformic acid, flowers of benzoin, and flowers of benzamine (Ref. 1). Benzoic acid occurs in the free form and as salts in various plants, especially in balsams and resins obtained from coal tar. It also occurs as hippuric acid (benzoyl glycine) in the urine of nearly all vertebrates. Formerly, benzoic acid was obtained from benzoin and hippuric acid. In present-day manufacturing processes, it is synthesized from a variety of starting compounds, such as toluene, benzaldehyde, benzotrichloride etc. (Refs. 1 and 2).

Benzoic acid consists of white crystals, scales, or needles that have a

slight aromatic odor. It is somewhat volatile at warm temperature and in steam. One gram dissolves in about 300 mL water, 3 mL alcohol, 5 mL chloroform, and 3 mL ether. It melts at about 122° C. Benzoic acid may be found free in nature. Gum benzoin may contain up to 20 percent benzoic acid. Most berries contain about 0.5 percent benzoic acid. It has been used as a preservative for foods and cosmetics and has been also used in a concentration of 6 percent in combination with 3 percent salicylic acid as an antifungal agent. It has varying degrees of antimicrobial activity. Benzoic acid is used as a buffering agent and a pharmaceutical necessity in some OTC products. Use of benzoic acid is permitted as a bacteriostatic agent in certain foods and medicinal products (Ref. 3).

(1) *Safety.* The Panel concludes that benzoic acid is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid alone is a mild irritant to the skin, eyes, and mucous membranes. Gosselin et al. (Ref. 4) rate the toxicity of benzoic acid as 3, which is a low rating. The mean lethal dose (LD_{50}) of benzoic acid in dogs and cats is 2 g/kg. In rats the intravenous LD_{50} is 1.7 g/kg. Tremors and convulsions preceded death in poisoned animals.

In one study on toxicity, the oral daily administration of benzoic acid to rats in dosages of 70 to 80 mg/kg caused an increase in mortality, decrease in weight gain, and decrease in resistance to stress (Ref. 5). Additive toxicity was noted when sodium bisulfite, another food preservative, was combined with benzoic acid.

The toxicity of benzoic acid for man has not been established. A 67-kg man ingested doses of 50 g benzoic acid without ill effects. Large oral doses produce gastric pain, nausea, and vomiting. In nine patients treated with 1.5 g benzoic acid twice daily up to a total of 12 g, gastric burning and anorexia resulted, but no renal impairment was observed. When benzoic acid or benzoate are ingested they conjugate with aminoacetic acid (glycine) and appear in the urine chiefly as hippuric acid. This conversion takes place in the liver. The ability to form hippuric acid from benzoic acid has been used as the basis for estimating liver function, particularly the ability of the liver to detoxify chemical substances. Benzoic acid is an irritant to the mucous membranes and cannot be administered internally without manifestations of gastric irritation. The neutral benzoates, on the other hand, are well tolerated in doses of 6 g or more.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of benzoic acid as a OTC antimicrobial agent for topical use on mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Benzoic acid is effectively germicidal against certain microbial strains. Goshorn, Degering, and Tetrault (Ref. 6) found that at a pH of 3.5, a 1:800-solution of benzoic acid kills both *Escherichia coli* and certain strains of staphylococci within an hour. At a pH of 5, however, it is not certain that benzoic acid is still bactericidal. At a strength of even 1:20 and pH 5, it will kill these organisms. Benzoic acid will inhibit bacterial growth in a concentration of 1:3,000 at this pH. The antimicrobial action of benzoic acid is chiefly, if not exclusively, due to the un-ionized portion of the molecule since benzoate ions permeate living cells with difficulty. A combination of 6 percent benzoic acid and 3 percent salicylic acid in an ointment base, commonly known as Whitfield's ointment, has fungistatic and fungicidal properties. The ointment causes exfoliation of the upper layers of the skin by the keratolytic action of the salicylic acid. A hyperemia characterizes the dermatomycosis and the fungi are cast off with the stratum corneum when the cells desquamate. It is doubtful that the benzoic acid plays an active role in this action since most of the keratolysis is due to the salicylic acid.

Benzoic acid forms salts with sodium hydroxide and other bases. The sodium salt is the most common one in use. Sodium benzoate is ionized, does not penetrate living cell membranes, and is not effective as an antimicrobial agent. the antiseptic activity of sodium benzoate is practically nil. The antiseptic activity of benzoic acid is due to the fact that it is an acid, poorly ionized, lipid soluble, and penetrates living cells.

Reports in the literature published between 1933 and 1950 appear to lend questionable support to the effectiveness of benzoic acid as an individual component in certain preparations used as rinses for the oral cavity (Ref. 7). A report by Barbour and Vincent (Ref. 8) describes the inhibition of *Bacterium aerogenes* and *Aspergillus niger* by benzoic acid. Accumulation of the ingredient at the cell surface with the resultant inhibition of microbial growth was greater with benzoic acid than with phenol and other antimicrobial compounds tested. Since the inhibition is a reversible phenomenon, such drugs are unlikely to exert any lasting influence on the flora of the oral cavity. Moreover, neither of the two organisms is representative of those present in the oral cavity. *Bacterium aerogenes* is seldom found in the mouth in appreciable numbers, and *Aspergillus niger* is not recognized as a constituent of indigenous oral flora.

Another study (Ref. 9) merely suggests that benzoic acid might be more useful as a selective medium to be used to isolate fungi from the air by inhibiting growth of airborne bacteria. This comment appears irrelevant to the effectiveness of benzoic acid in the preparations for use in the oral cavity.

A third report by Baldinger and Nieuwland (Ref. 10) described a study comparing the inhibition of *Bacillus coli* by benzoic acid and a series of alpha phenylsubstituted acids. In general, the latter exerted a greater inhibitory effect. This report is irrelevant as far as data pertaining to the effectiveness of benzoic acid in preparations used as rinses in the oral cavity is concerned.

Goshorn, Degering, and Tetrault (Ref. 6) demonstrated that benzoic acid is less active at alkaline or neutral pH than at acid pH. The test organisms studied were *Escherichia coli* and *Staphlyococcus aureus.*

Wyss and Poe (Ref. 11) studied the comparative efficacy of various antimicrobial agents using the FDA phenol coefficient technique. Benzoic acid had a coefficient of 5.3 against *Salmonella typhosa,* but it was no more active than phenol against *Staphylococcus aureus.* This test procedure, in use in 1931, was modified in 1950 because it did not distinguish between bacteriostatic and bactericidal activity. The modified test is not considered applicable to gargles, mouth rinses, and other preparations used in the oral cavity because it is difficult to simulate the flora commonly found in the oral cavity in vitro.

The Panel concludes from the foregoing data that benzoic acid possesses some bacteriostatic and bactericidal antimicrobial activity.

The Panel, however, concludes that there are insufficient data from controlled studies to establish the effectiveness of benzoic acid as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use of 0.1- to 0.3-percent concentration of benzoic acid in the form of a rinse, mouthwash, or syrup not more than

three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicriobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, pp. 132–133, 1968.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 186–187, 1973.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1164–1165, 1975.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 137, 1876.

(5) Shtenburg, A. J., and A. D. Ignatev, "Toxicological Evaluation of Some Combinations of Food Preservatives," *Food and Cosmetics Toxicology,* 8:369–380, 1970.

(6) Goshorn, R. H., E. F. Degering, and P. A. Tetrault, "Antiseptic and Bactericidal Action of Benzoic Acid and Inorganic Salts: Effect of pH," *Industrial and Engineering Chemistry,* 30:646–648, 1938.

(7) OTC Volume 130008.

(8) Barbour, R. G. H., and J. M. Vincent, "The Bacteriostatic Action of Phenol, Benzoic Acid and Related Compounds on *Bacterium aerogenes," Journal of General Microbiology,* 4:110–121, 1950.

(9) Eastwood, T. M., "Bacteriostatic and Fungistatic Action of Some Organic Chemicals," *Science,* 100:10–11, 1944.

(10) Baldinger, L. H., and J. A. Nieuwland, "The Relation of Some Physical Properties to Bactericidal Action of some alpha-Phenylsubstituted Acids," *Journal of the American Pharmaceutical Association (Scientific Edition),* 22:711–716. 1933.

(11) Wyss, A. P., and C. F. Poe, "Study of the Germicidal Values of Benzoic Acids and Benzoates," *Proceedings Institute of Food Technologists,* 6:21–28, 1945.

d. *Carbamide peroxide in anhydrous glycerin (urea peroxide).* The Panel concludes that carbamide peroxide is safe, but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Carbamide peroxide is a relatively stable complex formed by the union of urea with hydrogen peroxide. The compound is also known as urea hydrogen peroxide. Urea is the diamide of carbonic acid; for this reason the compound is also known as urea carbamide. Other names that have been used for urea hydrogen peroxide in the past are hyperal, perhydrit, and perhydrol urea. Its empiric formula is $CO(NH_2)_2.H_2O_2$ and its molecular weight is 94.0. The hydrogen peroxide content of the molecule is 34 to 35 percent of its total weight. The compound is a white crystalline powder that breaks down, if allowed to stand in air, into urea, oxygen, and water. It decomposes to urea and hydrogen peroxide in aqueous solution. One part carbamide peroxide is soluble in 2.5 parts of water. It is soluble in anhydrous glycerin and the complex is stable in glycerin as long as moisture is excluded. Carbamide peroxide is partly decomposed by alcohol and ether into hydrogen peroxide and urea. It is used for the extemporaneous preparation of hydrogen peroxide in the field, for travelers, etc. (Ref. 1).

Carbamide peroxide releases hydrogen peroxide which is decomposed by hydroperoxidases, peroxidases, and catalase present in the tissues, wounds, and saliva, and in bacteria. Catalase causes the release of atomic or "nascent" oxygen, a strong oxidizing agent which is presumed to exert an antimicrobial action before its conversion to diatomic molecular oxygen (O_2). The peroxidases induce rapid conversion of urea hydrogen peroxide to peroxide. Breakdown of the hydrogen peroxide to oxygen and water causes formation of bubbles of gas and foaming. This release of oxygen foam accounts for the debriding effect of peroxides. The urea exerts no significant proven therapeutic effect. In addition to anhydrous glycerin, carbamide peroxide is also soluble in propylene glycol.

(1) *Safety.* The Panel concludes that carbamide peroxide is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Although data on the safety of carbamide peroxide is sparse, it is the consensus of the panel that carbamide peroxide is safe. There were no data available in standard textbooks references in the literature, or in Panel submissions on acute, subacute, or chronic studies in animals or humans (Refs. 2, 3, and 4). There are no available data on irritation and hypersensitivity reactions, teratogenicity, or carcinogenicity attributed to the compound. One manufacturer presented evidence from 3,000 prescriptions and claimed that there were no adverse reactions in humans from use of the preparation. This was the only human study concerning adverse or toxic reactions (Ref. 5).

The Panel acknowledges that urea is a naturally occurring substance in the body, and that hydrogen peroxide, in concentrations of less than 3 percent, is safe for use in the mouth and throat. The Panel also recognizes that as soon as the combination of urea and peroxide comes in contact with living tissues, it is decomposed into urea and hydrogen peroxide. The Panel therefore, concludes that it is safe.

Since urea hydrogen peroxide is combined with glycerin, the Panel has made its judgment on the preparation dissolved in anhydrous glycerin. Clinical use and marketing experience has confirmed that carbamide peroxide in glycerin is safe in the dosage form proposed for use in the oral cavity.

There are reportred clinical studies in which the carbamide peroxide inanhydrous glycerin was used in inflammatory and otic conditions. It was found to be nontoxic, nonirritating, and nonsensitizing, and no adverse reactions were reported. Carbamide peroxide has been used in animals with no reported toxicity or irritation. However, the Panel cautions that concentration of hydrogen peroxide are toxic to the soft tissues and the oral cavity, and that rapid release of hydrogen peroxide from urea hydrogen peroxide could be toxic locally.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of carbamide peroxide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The proposed antimicrobial mechanism of action of carbamide peroxide is that it releases hydrogen peroxide. This is discussed in detail elsewhere in this document (See part IV. paragraph B.3.m. below—Hydrogen peroxide.)

Urea is a product of protein metabolism and allegedly aids in debriding necrotic tissues. Urea is a waste product that is found in human urine in concentrations of about 2 percent. It is a white, pure crystalline

material that is odorless and nontoxic. It was the first organic substance synthesized. A 2-percent solution has been recommended for treating external suppurating wounds. Urea allegedly prevents infections and stimulates cleansing and healing. However, data to substantiate this claim are lacking.

The Panel concludes that these are insufficient data available from controlled studies to establish the effectiveness of carbamide peroxide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 9.0- to 15.0-percent concentration of carbamide peroxide in anhydrous glycerin or propylene glycol in the form of drops or as a swab. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B. 3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care anitmicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windhoz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1266, 1976.

(2) OTC Volume 130037.

(3) OTC Volume 130085.

(4) OTC Volume 130017.

(5) OTC Volume 130016.

(6) Harvey, S.C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 997, 1975

e. *Cetalkonium chloride.* The Panel concludes that cetalkonium chloride is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Cetalkonium chloride ($C_{25}H_{46}ClN$) is also known as cetyldimethylbenzylammonium chloride, N-hexadecyl-N,N-dimethylbenzenemethanaminium chloride, benzylhexadecyldimethylammonium chloride, and hexadecyldimethylbenzylammonium chloride. Cetalkonium chloride has a molecular weight of 396.12.

Cetalkonium chloride is soluble in water, alcohol, acetone, ethyl acetate, propylene, and carbon tetrachloride. The pH of the aqueous solution is 7.2. Cetalkonium chloride is a cationic quaternary ammonium surfactant which is used as an antibacterial agent and fungicide. It is used in leather processing, textile dyeing, and as a mildew preventive in silicone-based water repellents. It is comparable with many nonionic detergents and is active in moderately alkaline solutions. Cetalkonium chloride water is odorless and practically tasteless at a 1:2,000 dilution (Ref. 1).

(1) *Safety.* The Panel concludes that cetalkonium chloride is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Studies included in a product submission have demonstrated that cetalkonium chloride, in a dose of 5 mg/kg, had a depressor effect upon the blood pressure of three dogs anesthetized with sodium barbital (Ref. 2). The prior injection of atropine apparently had no inhibitory effect on the vasodepression produced by the drug. Single intravenous doses of cetalkonium chloride equal to 17.3 and 20 mg/kg were toxic to 50 percent of the animals when tested in mice and rats, respectively. Cetalkonium chloride was found to have an oral LD_{50} value of 725 $\pm$ 20 mg/kg in the mouse and 990 $\pm$ 91 mg/kg in the rat. Subacute toxicity tests were carried out in mice, rats, and rabbits for periods of 14 days. It was concluded that cetalkonium chloride was more toxic by repeated administration than by single dose. Chronic toxicity studies were carried out in dogs for 14 weeks. Cetalkonium chloride retarded growth slightly, but no hematologic or pathologic changes which could be attributed to medication with the drug were observed. Solutions of cetalkonium chloride of 1:1,000 were found to be nonirritating to the bladder mucosa and oral mucosa of rabbits. Dilutions of 1:2,000 to 1:4,000 instilled into the rabbit eye produced mild to moderate irritation. The following morning, the eyes were still slightly irritated. In three cases the 1:3,000 dilution produced a mild irritation, but all eyes appeared normal the following morning. The 1:4,000 dilution produced a mild irritation in one rabbit, and only a slight irritation in two other rabbits. It appeared to be normal the following morning.

Data on tumorigenic, mutagenic, and teratogenic effects after long-term use in mouthwashes, gargles, and rinses are not available. Data on teratogenic effects on daily use of mouthwashes during pregnancy are not available.

(2) *Effectiveness.* The Panel concludes that there are insufficient data to permit final classification of the effectiveness of cetalkonium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Industry researchers in a study incorporated in a submission to the Panel performed both in vitro and in vivo testing of cetalkonium chloride (Ref. 2). Samples of saliva were collected from several normal human subjects, pooled, and warmed to 37° C. Samples of 0.5 mL of saliva were transferred to sterile culture tubes and 2mL of undiluted mouthwash, previously warmed to 37° C, were added. The final concentration of saliva was 20 percent. Subcultures were made at intervals of 15, 30, 60, 90, 120, and 300 seconds after the addition of the mouthwash. They reported that normal saliva failed to show growth of bacteria after 15 seconds exposure to the cetalkonium chloride mouthwash. These results are open to criticism in that pooled saliva cannot be standardized from laboratory to laboratory and, therefore, should not be used. In addition, no inactivating medium was used as recommended in the in vitro test suggested by the Panel. The same authors, in order to compare cetalkonium chloride to other nonquaternary mouthwashes under conditions of actual use, carried out experiments on normal subjects to measure the percentage reduction of bacteria in the mouth following the use of various mouthwashes. According to these authors, cetalkonium chloride produced a reduction of over 90 percent in the number of flora in the oral cavity for at least 30 minutes after medication. These results are also open to criticism because no inactivating medium was used as recommended in the in vitro test suggested by the Panel.

Cetalkonium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

Much of the literature forwarded to the Panel in the form of industry submissions was not pertinent to cetalkonium chloride (Ref 2).

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of cetalkonium chloride as

an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 253, 1976.

(2) OTC Volume 130073.

f. *Cetylpyridinium chloride.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of cetylpyridinium chloride as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cetylpyridinium chloride is a quaternary nitrogenous compound derived from pyridine (Ref 1). Pyridine is a six-membered heterocyclic structure containing a trivalent nitrogen atom at the number one position in the ring. Conversion of the nitrogen atom to a pentravalent state permits addition of a hexadecylradical or other side chain and a hydroxyl, chloride, or bromide anion to the nitrogen atom, forming quaternary nitrogenous compounds. These are referred to as pyridinium derivatives. They have five bonds, four negative that form covalent bonds with organic radicals and one positive that results in an ionic type of bonding. (See part IV. paragraph A.8.b. above—The pyridinium compounds.)

A hexadecyl (cetyl) radical is substituted for a hydrogen atom on position one and a hydroxyl group bonds with the positive charge to form a base. When dissolved in water, it ionizes into a quaternary pyridinium ion and a hydroxyl ion. It interacts with acids such as hydrochloric to form salts. The chloride is a commonly used salt. Cetylpyridinium chloride is 1-hexadecylpyridinium chloride and contains, on the anhydrous basis, not less than 99 percent of $C_{21}H_{38}ClN$, it may be prepared by interaction of cetyl chloride and pyridine under pressure at an elevated temperature (Ref 2).

Cetylpyridinium chloride is a white powder, with a slight, characteristic odor (Ref 2). The salt is available as the monohydrate. Cetylpyridinium chloride melts at from 77 to 82° C. It is freely soluble in water, alcohol, chloroform, but it is not soluble in ether and benzene (Ref 3). A 1-percent solution is neutral to litmus, but when pH is determined with a glass electrode, it ranges between 6 and 7. The surface tension of a 0.1-percent aqueous solution at 25° C is 43 dyn/cm, a 1-percent aqueous solution is 41 dyn/cm, and a 10-percent aqueous solution is 38 dyn/cm (Ref 3).

The cetyl radical confers lipophilic qualities to the compound as is the case with multicarbon radicals in other quaternary nitrogenous compounds. This sets the balance between the lipophilic-hydrophilic attributes of quaternary nitrogenous compounds necessary for antimicrobial activity.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of cetylpyridinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The minimum lethal does for cetylpyridinium chloride in rabbits tested by injection was 20 mg/kg, and the average lethal does was found to be 35 mg/kg (Ref. 4). It is more toxic when instilled intraperitoneally (Ref 4). The LD_{50} is 250 kg/mg subcutaneously, 6 mg/kg intraperitioneally, 30 mg/kg intravenously, and 200 mg/kg orally (Ref 5). When 50 mg/kg in water were administered daily for 60 days to rats, no toxic effects or alteration in the rate of growth of the animals were noted (Ref 5). Doses of 5 to 10 mg/kg administered through the esophagus showed no toxic effects over a 60-day period (Ref 5).

The toxic systemic effects of cetylpyridinium chloride are similar to those of other quarternary nitrogenous compounds and are described below.

A 1:3,000 solution of cetylpyridinium is irritating to the mucous membranes of the conjunctiva, but not when applied to the skin (Ref. 6). A 1:200 alcoholic or aqueous solution of cetylpyridinium does not cause skin irritation (Ref. 7). Although concentrated aqueous solutions are primarily skin irritants, percutaneous absorption is not believed to be significant (Ref. 8). Allergic manifestations have not been reported, but the Panel warns that the cetylpyridinium chloride can act as a hapten and cause sensitization.

The human fatal dose for the quaternary nitrogenous compounds has not been established, but has been estimated to be between 1 and 3 g for an adult (Ref. 8). Toxic doses of cetylpyridinium chloride manifest an autonomic (nicotinic) blocking effect on the ganglia and a curariform (muscarinic) type of response. The principal manifestations of poisoning from oral ingestion are vomiting, collapse, and coma (Ref. 8). Local gastrointestinal irritation, restlessness, apprehension, confusion, dyspnea (labored breathing), and cyanosis occur followed by convulsions, muscle weakness or paralysis, and death due to paralysis of respiratory muscles (Ref. 8). The nicotine-like effects of blocking the autonomic ganglia are most likely due to the curariform action and are similar to those manifested by many quaternary nitrogenous compounds (Ref. 9). Ordinarily, salts of quaternary nitrogenous compounds do not penetrate epithelial barriers because they are not lipophilic and are highly ionized. The presence of a high molecular weight lipophilic group on the molecule of these quaternary nitrogenous compounds increases their lipid solubility and facilities penetration through cell membranes. The lipophilic group enhances its degree of absorption.

Data on cumulative effects, metabolism, and excretion of cetylpyridinum chloride in man, particularly after long-term use, are not available. Data on tumorigenic, mutagenic, and teratogenic effects when used on a daily basis for months or years in mouthwashes and other oral health care products are not available. Data on teratogenic effects if used during pregnancy are not available. Clinical experience following prescription and OTC use of the ingredient have not thus far revealed any overt toxic manifestations.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness cetylpyridinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cetylpyridinium chloride has the same detergent and antiseptic actions characteristic of other quaternary nitrogenous compounds, i.e., benzalkonium chloride and benzethonium chloride, that manifest antimicrobial activity (Ref. 2). The compound was introduced for clinical

use in 1942. Cetylpyridinium chloride is bactericidal and bacteriostatic against may gram-positive and some gram-negative organisms. A 1:50,000 aqueous solution will kill staphylococci in 10 minutes, though not in 5 minutes (Ref. 10). It is also active against some fungi, including *Candida albicans,* and against *Trichomonas vaginalis* (Ref. 2). Cetylpyridinium chloride's action is uncertain or it is ineffective against spores and most viruses. Its activity is diminished by the presence of serum, tissue fluids, proteins, lipids, and phospholipids (Ref. 2). Soaps, other anionic sufactants, and detergents are incompatible with cetylpyridinium chloride and antagonize its action (Ref. 2). Cetylpyridinium Chloride lowers surface tension and has wetting and emulsifying properties similar to other quaternary nitrogenous compounds (Ref. 2).

When applied to the skin, cetylpyridinium chloride and other quaternary ammonium antiseptics form a film under which bacteria may remain viable even though the outer surface of the film is bactericidal and sterile (Ref. 2).

Cetylpyridinium chloride in a concentration of 1:100 is used topically for preoperative disinfection of intact skin. A 1:100 solution has been used for prophylactic antisepsis of superficial wounds. A 1:5,000 to 1:10,000 solution has been used for therapeutic disinfection of mucous membranes. Cetylpyridinium chloride is used as an active ingredient in mouthwashes, rinses, and gargles. It is also incorporated into lozenges with the intent of obtaining an antimicrobial action on the mucous membranes of the mouth and throat (Ref. 2).

The antimicrobial spectrum of cetylpyridinium chloride is limited. This is made more so by the uncertainty imposed by environmental factors during use, such as the presence of proteins, neutralizing anions, and organic material and debris in the mouth. Furthermore, there is sufficient evidence from long-term clinical experience that the topical application of antimicrobial agents to infected and inflamed areas is of doubtful therapeutic value, is not curative, and may even aggravate an inflammatory state. The Panel notes that there are no data to justify the use of cetylpyridinium choride in oral health care products on a continuing day-to-day basis for protracted periods of time for prophylaxis and other uses when no symptoms are present and no therapeutic benefit can be demonstrated. The Panel concludes that even though cetylpyridinium chloride does kill or inhibit certain select microorganisms found in the oral flora, there are insufficient data to demonstrate that this antimicrobial activity is of therapeutic benefit in treating sore mouth or sore throat or both.

Cetylpyridinium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of cetylpyridinium chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025- to 0.1-percent concentration of cetylpyridinium chloride in the form of a rinse, mouthwash, or gargle not more than three to four times daily. Use a 0.025- to 0.1-percent concentration of cetylpyridinium chloride in the form of a lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling).

(5) *Evaluation.* Data to demontrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 148, 1957.

(2) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott Co., Philadelphia, p. 259, 1960.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 254, 1976.

(4) OTC Volume 130007.

(5) Nelson, J. W., and S. C. Lyster, "The Toxicity of Myristyl-gamma-Picolinium Chloride," *Journal of American Pharmaceutical Association (Scientific Edition),* 35:89–94, 1946.

(6) Warren, M. R., et al., "Pharmacological and Toxicological Studies on Cetylpyridinium Chloride, A New Germicide," *Journal of Pharmacology and Experimental Therapeutics,* 74:401–408, 1942.

(7) Clarke, G. E., "Skin Sterilization With Cetyl Pyridinium Chloride," *The Urologic and Cutaneous Review,* 46:245–246, 1942.

(8) Arena, J. M., "Poisonings and Other Health Hazards Associated With Use of Detergents," *Journal of the American Medical Association,* 190:56–58, 1964.

(9) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section III, pp. 197–200, 1969.

(10) Kolloff, H. G., et al., "Germicidal Activity of Some Quaternary Ammonium Salts," *Journal of the American Pharmaceutical Association (Scientific Edition),* 31:51–53, 1942.

g. *Chlorophyll.* The Panel concludes that chlorophyll is safe, but that there are insufficient data available to permit final classification of the effectiveness of chlorophyll as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Chlorophyll is the green pigment and photosynthetic agent found in plants. Functionally, it is comparable to hemoglobin found in animal life in that it sustains respiration in plants. Chlorophyll is not a single entity, but is found in three forms: a, b, and c. Higher phyllogenetic orders of plants with green leaves and green algae contain chlorophyll a and chlorophyll b in the approximate ratio of 3:1. Chlorophyll c is found together with chlorophyll a in many types of marine algae.

Chlorophyll a is freely soluble in ether, ethanol, acetone, chloroform, carbon disulfide, and benzene. The alcoholic solution is blue-green with a deep red fluorescence (Ref. 1). Chlorophyll b is freely soluble in absolute alcohol and ether. The ether solution has a brilliant green color. Solutions with other organic solvents are usually green to yellowish-green with red fluorescence (Ref. 2).

The chlorophyll of commerce is an intensely dark-green aqueous, alcoholic, or oil solution. It is made from dehydrated alfalfa and broccoli leaves.

Careful alkaline hydrolysis of chlorophyll replaces the methyl and phytyl ester groups with sodium or potassium. The resulting salts are called chlorophyllins and are water soluble. Water-soluble sodium and potassium salts occur as a blue-black glistening powder having a fishy odor. They are slightly soluble in alcohol and freely soluble in water. A 1-percent solution in water is dark green and alkaline, having a pH range of 9.5 to 10.7.

Chlorophyll was introduced into clinical medicine in 1945. It is similar to hemoglobin, structurally different in that magnesium replaces iron in the complex of the pyrrole rings. Chlorophyll and its derivatives are used to color soaps, oils, fats, waxes, confectionery, preserves, liquors, cosmetics, and perfumes. It is also used as a deodorant.

The Panel reviewed a submission on a currently marketed product which contained both safety and effectiveness data on chlorophyll (Ref. 3).

(1) *Safety.* The Panel concludes that chlorophyll is safe as an OTC antimicrobial agent for topical use on mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Cholorphyll and its derivatives have little or no toxicity when applied topically, taken orally, or injected intravenously (Ref. 4). Chlorophyll is found in all green-colored plant life, and inasmuch as leaves and grasses serve as food and are consumed in large quantities in the diets of herbivorous and omnivorous animals, it is not unreasonable to assume that chlorophyll is nontoxic when used topically, orally, or intravenously. A potassium-sodium-copper complex of chlorophyll fed to rats in a concentration of 3 percent of their diets for life showed no signs of toxicity for the complex including copper (Ref. 5). Sensitization has not been reported following its use topically or when ingested orally.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of chlorophyll as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Chlorophyll has been used in aqueous solutions as a deodorant to overcome mouth odor. The mechanism of its alleged action as a deodorant has never been clearly defined, and the ingredient has fallen into disuse over recent years since it has not been demonstrated that it is an effective deodorant. In dogs, doses of 30 to 150 mg decreased halitosis; however, the ingested chlorophyll had no effect on the odor in the dogs' coat (hair) in the animals tested. It allegedly promotes wound healing, but no data were submitted or are available from controlled studies to substantiate that this occurs.

The water-soluble chlorophyllins appear to have some bacteriostatic properties in vitro. The concentration necessary for this inhibition is often 1:80 or more; however, all pathogens are not affected to the same degree. In vivo, the bacteriostatic influence of these chlorophyllins is supposedly due to the production of an unfavorable environment rather than to a direct action of the agent on the metabolic activity or cell structure of the pathogens (Ref. 4).

There is no evidence that chlorophyll derivatives are bactericidal. Insufficient data were submitted concerning the effectiveness of chlorophyll as an antimicrobial agent for the relief of symptoms of sore mouth and sore throat.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of chlorophyll as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.2- to 0.5-percent concentration of chlorophyll in aqueous solution in the form of rinses, mouthwashes, gargles, sprays, or swabs not more than three to four times daily. Use a 0.2- to 0.5-percent concentration of chlorophyll in the form of a tablet or lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Anderson, A. F. H., and M. Calvin, "An Improved Method for the Separation and Purification of Chlorophyll a," *Nature,* 194:285-286, 1962.

(2) Dougherty, R. C., et al., "Structure of Chlorophyll c," *Journal of the American Chemical Society,* 88:5037-5038, 1966.

(3) OTC Volume 130015.

(4) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 11th Ed., C. V. Mosby Co., St. Louis, p. 422, 1956.

(5) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1629, 1955.

h. *Dequalinium chloride.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of dequalinium chloride as OTC antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium is a base derived from 2-methylquinoline. Methylquinoline may be quaternized to form a series of quinaldinium compounds. When the trivalent nitrogen is converted to the pentavalent form, a hydrogen atom on the nitrogen atom of the quinaldine base may be substituted by an alkyl radical. In dequalinium, a nitrogen atom is attached at each end of a decamethylene chain. Thus, the dequalinium molecule has two quaternary nitrogen atoms, one at each pole of the chain. This chain serves as the lipophilic portion of the molecule. The two quinaldinium groups at each end are ionized into quaternary cations. Dequalinium, therefore, is similar in chemical, physical, and pharmacologic properties to other quaternary nitrogenous compounds.

Dequalinium acetate is 1,1'-decamethylenebis[4-aminoquinaldinium acetate]; dequalinium chloride is the chloride of the same quaternary base (Ref. 1). It is a white or pinkish-buff, slightly hygroscopic powder. One gram dissolves in about 2 mL water and in 12 mL alcohol. It melts, with decomposition, at about 280°C.

Dequalinium chloride is a creamy-white powder. It is slightly soluble in water (1 g in 20 mL). One gram dissolves in about 200 mL propylene glycol. It melts, with decomposition, at about 315°C.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of dequalinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium has a low degree of toxicity similar to other "quats." The lethal dose for humans is not known, but is believed to be from 3 to 5 g. No data on acute animal or chronic toxicity in humans were submitted to the Panel. The incidence of sensitization is low. Concentrated solutions can be irritating to the skin. Data on its absorption from the mucous membranes, metabolic fate, or excretion are not available. The Panel was not furnished with data from controlled studies concerning tumorigenic, mutagenic, or teratogenic effects when used on a daily basis in the mouth and throat for months or years at a time in mouthwashes and similar oral health care products. No data are

available on teratogenic effects when used during pregnancy.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of dequalinium chloride as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Dequalinium acetate and chloride are antibacterial and antifungal agents. They are active against many gram-positive and gram-negative bacteria, also against *Borrelia vincenti, Candida albicans,* and several trichophyton species. Their activity is little affected by serum.

The chloride is applied locally in a variety of preparations (Ref. 2). For infections of the mouth, gums, and throat, it is used in lozenges containing 0.25 mg, or applied as a 0.5-percent paint in propylene glycol. For monilial or trichomonal vaginitis it is employed in pessaries containing 10 g. For infected skin lesions, burns, or wounds, a cream containing 0.4 percent of dequalinium chloride is applied; 0.25 percent of prednisolone may be added. Dequalinium acetate, which is much more soluble in water, is used in medicated gauze dressings.

The dequalinium salts are incompatible with soap and other anionic surface-active agents; they are also incompatible with phenol and chlorocresol.

The Panel has no submission from any firm of any product containing either of these salts. The Panel feels that dequalinium chloride is of limited clinical usefulness as a topical antimicrobial agent for the temporary relief of occasional symptoms of sore mouth or throat because its antimicrobial spectrum is limited and made more so by the uncertainty imposed by environmental factors such as the presence of proteins, neutralizing anions, and organic material in the mouth. Furthermore, the evidence is overwhelming that the topical application of antimicrobial agents to infected an dinflamed areas is of doubtful therapeutic value, is not necessarily curative, and may even aggravate an inflammatory state. Antimicrobial agents are of value for certain infections for which the agent is specifically microbicidal. Such special conditions can only be diagnosed by a physician or dentist and are not amenable to self-diagnosis or treatment such as would be the case for OTC products.

Dequalinium chloride manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel does not recommend mouthwashes, rinses, sprays, or lozenges containing antimicrobial agents for deodorizing, cleansing, or prophylaxis, or for oral health care on a daily basis or for use for protracted periods particularly in situations that are devoid of symptoms. (See part IV. paragraph A.2. above—Antimicrobial agents for use in the oral cavity.)

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of dequalinium acetate and chloride as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.5-percent solution of dequalinium chloride in propylene glycol. Apply by swabbing locally to lesions in the mouth and throat not more than three to four times daily. Use a lozenge containing 0.25 mg of dequalinium chloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above-Cateogory I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care animicrobial agents. (See part IV. pargraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ. p. 381, 1976.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 396, 1973.

i. *Domiphen bromide.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of domiphen bromide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Domiphen is a quaternary ammonium compound. It is a base that forms salts with acids. The bromide is the salt used for antimicrobial purposes. Chemically it is N,N-dimethyl-N-(2-phenoxyethyl-1-dodecanaminium bromide; dodecyldimethyl (2-phenoxyethyl) ammonium bromide; (beta-phenoxyethyl) dimethyldodecylammonium bromide, ($C_{22}H_{40}BrNO$) (Ref. 1). Domiphen bromide is a white crystalline substance. The crystals have a mild, characteristic odor, a bitter taste, and are freely soluble in water (100 g/mL). Domiphen bromide is soluble in alcohol, acetone, and chloroform, but only slightly soluble in benzene. At 25° C the pH of a 10.0-percent aqueous solution is 6.42, the 1.0-percent solution 5.5, and the 0.1-percent solution 6.8. As is the case with other quaternary nitrogenous compounds, salts of domiphen are surface-active agents with detergent and surface tension-reducing properties. The salts ionize when dissolved in water and the cation is the active ion. The surface tension value of the 10-percent aqueous solution at 25° C is 26.75 dyn/cm and the 0.1-percent 22.08 dyn/cm. Aqueous solutions are clear and colorless and foam profusely on shaking. Solutions are incompatible with anionic agents, particularly soaps.

Domiphen bromide is a member of a large group of quaternary ammonium surface active compounds. They were widely used as disinfectants for inanimate objects but subsequently lost popularity as their limitations became apparent. To a lesser extent, certain members of the group have been used as skin antiseptics. Benzalkonium chloride, U.S.P., is probably the "quat" most extensively employed for this purpose, especially as a preoperative skin preparation prior to minor surgical procedures. The antimicrobial activity of the "quats" has been extensively reviewed by Lawrence and Block (Ref. 2).

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of domiphen bromide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The concentrations of domiphen bromide used in commercial lozenges and mouthwashes appear to be nontoxic. Kutscher and Budowsky (Ref. 3) stated that clinical use of a mouthwash containing 0.01 percent domiphen bromide two to six times daily for up to 52 weeks resulted in no apparent local or systemic toxicity.

There were 746 patients treated with this or other regimens of the same solution.

No local or systemic toxicity was attributable to 0.01-percent domiphen bromide when used as a mouth spray in 154 patients. The patients were all being treated for oral disease, and the duration of therapy varied from 2 to 42 days. An unspecified number of patients was placed on oral rinses 2 to 6 times per day for up to 52 weeks using 0.01 percent domiphen bromide solution. No toxicity was reported during or after this therapy (Ref. 3).

Patch-tests utilizing 1:1,000 solutions of domiphen bromide applied to the skin of 405 volunteers were negative after being in place for 24 hours. The solvent for domiphen bromide was not specified. These same individuals were retested 10 days later and again the responses were all negative (Refs. 4 and 5).

Six adverse reactions were reported between 1958 and 1970 for a lozenge product containing domiphen bromide. These included one complaint of lack of effectiveness. Other complaints included burns on the tongue (two cases), soreness of the mouth (one case), fungal growth after use (one case), and chalk-like taste (one case) (Ref. 5).

A number of animal studies have been conducted with regard to the safety of domiphen bromide. An unpublished study (Ref. 6) determined the intravenous LD_{50} for domiphen bromide to be 18 mg/kg for rats, 31 mg/kg for mice, and 11 to 12 mg/kg for rabbits. The intraperitoneal LD_{50} was 40 to 45 mg/kg for rats and 10 to 20 mg/kg for guinea pigs. The oral LD_{50} could not be determined since marked diarrhea resulted. Oral doses used were as high as 800 mg/kg with five of six unspecified laboratory animals surviving (Ref. 7). The pharmacological and toxicological effects of the various quaternary ammonium compounds are almost identical (Ref. 2). Toxic effects can be generalized and result in convulsions or produce central nervous system depression followed by death. The depression is due to the curare-like action of these compounds (Ref. 8).

The movement of frog cilia was inhibited after a 30-minute exposure to a 1:5,000 concentration of domiphen bromide. Daily instillation of a 1:5,000 solution in rabbit's eyes for 17 days resulted in no vasodilation of conjunctival vessels, no change in corneal reflex, and no histological abnormalities (Ref. 9).

Domiphen bromide was administered to white rats of both sexes by gastric intubation for 7 weeks. The dosage was 10 mg/kg daily for 5 days in each week. The animals showed an inability to gain weight comparable to litter-mate controls. No change was found in hematocrit values, red or white blood cell counts, or in the normal distribution of white blood cells. Also, no change in gut flora was found. No changes were found in the liver, kidney, adrenal, bone marrow, brain, heart, lung, spleen, thyroid, pituitary, ovaries, testes, pancreas, skeletal muscle, or retina (Ref. 7).

Six dogs were given domiphen bromide orally for 3 months. One group of three dogs was given 10 mg daily for 5 days per week. A second group of three dogs was given an escalating dosage of 5 mg/kg, then 20 mg/kg, and then 30 mg/kg. A control group was maintained. Vomiting and loss of appetite were noted at the higher doses. One dog demonstrated an atypical reduction in hemoglobin, hematocrit, and an erythrocyte count. No other toxicity or histopathologic changes were induced (Ref. 10).

There are no data from controlled studies on the tumorigenic or mutagenic effects of domiphen bromide when used in the mouth and throat on a regular basis for months and years as a mouthwash or for similar oral health care products. There are no data on its teratogenic effects if used during pregnancy.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of domiphen bromide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are many reports in the medical literature on the use of domiphen bromide as a skin disinfectant, for disinfecting raw sewage, and as an antimicrobial for use in the oral cavity. These studies, however, are in many cases subjective and uncontrolled. In the studies relevant to the use of domiphen bromide in the oral cavity, the exposure time at the stated concentration is unlikely to occur in the mouth because of salivary dilution.

Sturzenberger and Leonard (Ref. 11) evaluated the effects of a mouthwash containing domiphen bromide and cetylpyridinium chloride in combination on plaque reduction. Twenty-seven adults used their own toothbrush techniques in combination with a 30-second rinse of either the experimental or placebo mouthwash after brushing. After 1 week the experimental mouthwash showed a 38-percent decrease in stainable plaque as compared to either the placebo or a third mouthwash containing the cetylpyridinium chloride only. The Panel emphasizes that it is highly debatable that there is any well-established correlation between plaque reduction and antimicrobial activity in the mouth and does not consider these studies of significance as applicable to relief of the symptoms due to sore throat and sore mouth. This study also does not support the effectiveness of domiphen bromide because domiphen bromide was not tested as a single ingredient.

Gjermo, Baastad, and Rolla (Ref. 12) found that the plaque-inhibiting effects of the quaternary ammonium compounds in vivo did not correlate with their activity against salivary bacteria in vitro.

Shern, Swing, and Crawford (Ref. 13) compared the in vitro antimicrobial effects of chlorhexidine, a quaternary ammonium compound, with other surface-active compounds. They used the in vitro plaque assay system of McCabe, Keyes, and Howell (Ref. 14) to determine the minimum concentration of drug necessary to inhibit plaque formation by *Streptococcus mutans* and gram-positive filamentous strains. The quaternary ammonium compound benzalkonium chloride was approximately equal in plaque-inhibitory ability to chlorhexidine gluconate and significantly more effective than other compounds tested. As stated above the Panel does not regard these studies as proof of effectiveness of antimicrobial activity in the mouth.

Turesky, Glickman, and Sandberg (Ref. 15) evaluated the antiplaque effects of the quaternary ammonium compounds. These substances inhibited plaque growth. Saliva or pellicle did not affect the products' antibacterial activity.

Seidenberg (Ref. 16) demonstrated that domiphen bromide was effective as a skin disinfectant when the hands were washed for a 3-minute period in a 0.1-percent aqueous solution. Domiphen bromide was bactericidal at low levels against *Escherichia coli,* salmonella species, *Shigella dysenteriae, Staphylococcus aureus, Streptococcus hemolyticus,* and *Diplococcus pneumoniae.* Gram-positive bacteria were more sensitive than gram-negative strains and proteus species were resistant. It was noted that soaps and serum proteins markedly reduced the activity of domiphen bromide. This study by Seidenberg (Ref. 16) was carried out using a 0.1-percent solution of the same product which apparently represented a 1:1,000 concentration of domiphen bromide. This is 10 times the concentration of domiphen bromide in

the lozenge product and 20 times that contained in two other mouthwash products. For this reason this study is not relevant to the effectiveness of domiphen bromide as an antiseptic contained in mouthwashes or lozenges. The concentrations of domiphen bromide tested in vitro varied from experiment to experiment with no consistent protocol. However, when protein was present in the broth medium, a concentration of 0.015 percent (1:6,666) domiphen bromide was required to kill certain gram-positive bacteria, e.g., *Diphtheria bacilli,* and 2.5 percent (1:40) was necessary to kill certain gram-negative bacteria (Ref. 16). Currently marketed mouthwashes contain 1:20,000 domiphen bromide. The findings of Seidenberg (Ref. 16) do not support the antiseptic effectiveness of domiphen bromide.

Kutscher et al. (Ref. 17) studied the effect of domiphen bromide on 18 pathogenic strains of *Candida albicans.* After 17 hours of incubation, 3 of the 18 strains were inhibited by a 1:48,000 dilution of the compound, 2 of the 18 strains were inhibited by a 1:96,000 dilution, 12 of the 18 strains were inhibited by a 1:192,000 dilution, and 1 of the 18 strains was inhibited by a 1:384,000 dilution. The authors stated that an optimistic outlook on the possible clinical usefulness of domiphen bromide was justified on the basis of their results. The findings of Kutscher et al. (Ref. 17) of merely inhibiting *Candida albicans* by a 17-hour exposure to low concentrations of domiphen bromide has dubious signifiance relative to its generalized use as a mouthwash. While this yeast is a component of the indigenous oral flora, it is normally present in large numbers. Moreover salivary flow would certainly dilute the 0.005-percent (1:20,000) concentration of domiphen bromide found in commercially available mouthwash 10 times to 1:200,000 within 17 hours or less.

Scala and Vicari (Ref. 18) found the growth of *Stapylococcus aereus* to be inhibited for 48 hours by a 0.8 μg/mL concentration of domiphen bromide. A 1.2 μg/mL concentration inhibited the same organism for 72 hours. A concentration of 1.2 μg/mL also inhibited the growth of *Escherichia coli* for 72 hours. The inhibitory concentration indicated in this study for both organisms is approximately 1.0 μg/mL (0.001 mg/mL=1:1,000,000). Moreover, a 48- to 72-hour exposure time to such a concentration is unlikely to occur in the mouth because of salivary dilution.

Bavin, Kay, and Simmonite (Ref. 19) compared the antibacterial activity of domiphen bromide to other quaternary ammonium compounds and disinfectants. They found domiphen bromide to have a level of activity that is either equal to or better than benzalkonium chloride against *Staphylococcus aureus, Proteus vulgaris, Salmonella typhi, Klebsiella pneumoniae, Bacillus mycoides, Pseudomonas aeruginosa,* and *Clostridium tetani.* The bacterium which was least sensitive to domiphen bromide and the other quaternary ammonium compounds was *Pseudomonas aeruginosa.* The concentrations of domiphen bromide and the other quatenary ammonium compounds needed to kill the test bacteria increased when 10-percent serum was incorporated into the nutrient broth. However, the concentration of domiphen bromide needed to inhibit growth was less than benzalkonium chloride for all organisms except *Staphylococcus aureus* and *Bacillus mycoides.* In regard to these two bacterial strains, domiphen bromide was at least as active as the rest of the quaternary ammonium compounds. In a summary of their work, Bavin, Kay and Simmonite (Ref. 18) indicated domiphen bromide to be the most active of the different antiseptics which they studied. Partial inactivation occurred in the presence of soap or protein. This study, which was fairly well designed, took into account the need to utilize a large inoculation (10^7 microorganisms per test), the addition of particulate organic material to the domiphen bromide prior to exposure of the test organism and the use of an inactivator in the subculture medium employed to ascertain the bacterial activity. The use of the inactivator, polyethylene oxide, was not significant in the test results. This is not surprising because, since the paper's publication, better inactivators have been found. The addition of particulate organic material (killed yeast cells) to the test system demonstrated a reduction in the bactericidal activity of domiphen bromide of about 20- to 40-fold. With a 10-minute exposure, the bactericidal concentrations ranged from 100 mg/100 mL (0.1 percent=1:1,000) for *Staphylococcus Aureus* to 1000 mg/100 mL (1 percent=1:100 for *Proteus vulgaris.* These concentrations are greatly in excess of the 1:20,000 concentrations of domiphen bromide found in commercial mouthwashes.

The minimum inhibitory concentrations (MIC's) of domiphen bromide within 48 hours, in the absence of organic material, ranged from 1:8,000 to 1:32,000 for gram-positive bacteria and from 1:125 to 1:2,000 for the gram-negative organisms. In the presence of blood the MIC's were 1:4,000 for gram-positive organisms and 1:32 to 1:500 for gram-negative organism. These MIC's are generally much in excess of the 1:20,000 domiphen bromide concentration found in commercial mouthwashes.

Kutscher et al. (Ref. 20) tested domiphen bromide against 18 pathogenic strains of *Candida albicans.* The concentration of domiphen bromide used was 0.01 percent. It was found that all of the test organisms were killed in 5 to 10 minutes. While this paper implies killing of *Candida albicans* by 0.01 percent (1:10,000) domiphen bromide in 5 to 10 minutes, critical examination of the methodology reveals that the investigators did not distinguish between fungicidial and fungistatic activity. Moreover, 0.01 percent domiphen bromide is twice the 0.005-percent concentration employed in commercial mouthwashes.

Knusel and Loustalot (Ref. 21) compared the effect of domiphen bromide and sodium fluoride on streptococci isolated from carious lesions in the rat and on microorganisms found in the saliva and mouths of the animals. The animals used were from a caries-prone strain. When domiphen bromide and sodium fluoride were administered in the drinking water, the concentration of domiphen bromide which produced a 50-percent inhibition of caries was 20 mg percent while 8.8 mg percent of sodium fluoride produced the same effect. In a separate experiment, domiphen bromide (3 mg percent) inhibited caries in 7 percent of the animals while a level of 30 mg percent inhibited caries in 54 percent of the test animals. A concentration of 10 mg percent sodium fluoride prevented caries in 50 percent of the animals. In addition to the cariostatic effects of domiphen bromide in situ, the authors studied the compound's ability to inhibit cariogenic streptococci and other similar microorganisms in vitro. Domiphen bromide inhibited reproduction of the bacterial strains at very low levels. For the streptococcus species, the MIC ranged from 0.5 to 5μg/mL; for *Staphylococcus aureus,* the MIC was 5 μg/mL; for lactobacillus species, the MIC was 50μg/mL. Sodium fluoride, in contrast, inhibited the reproduction of the experimental bacteria only a very high doses (MIC's ranged from 100 to 1,000 μg/mL). The authors stated that the potent effect of domiphen bromide on gram-positive cocci is noteworthy. They felt that the marked effect of domiphen bromide on bacterial reproduction recommended it as a caries inhibitor. During a discussion of their

results, they concluded that domiphen bromide had a strong caries-inhibiting effect, which was only slightly inferior to that of sodium fluoride. In contrast to sodium fluoride, domiphen bromide was effective against cariogenic streptococci and other types of microorganisms found in the oral cavity. In this study the 20 mg percent (1:5,000), 30 mg percent (1:3,750) required to produce approximately 50 percent inhibition of caries in the test animal was apparently administered ad lib to the animals in their water supply. Obviously, such quantities greatly exceed what a human would receive in a domiphen bromide mouthwash used a few times daily. The methodology and results of the in vitro studies are difficult to interpret.

Adair, Geftic, and Gelzer (Ref. 22) determined the minimum inhibitory concentrations of domiphen bromide and five other quaternary ammonium compounds against *Pseudomonas aeruginosa* ATCC 9027. Domiphen bromide had an MIC equal to 50 μg/mg while alkyldimethyl-benzylammonium chloride had a MIC of 100 μg/mL, alkyldimethyl 3,4-dichlorobenzylammonium chloride had MIC of 200 μg/mL. Cetyltrimethylammonium bromide, cetyldimethylethylammonium bromide, and cetylpyridinium chloride all had MIC's greater than 1,000 μg/mL. When resistance to alkyldimethylbenzylammonium chloride was developed in *Pseudomonas aeruginosa* ATCC 9027, the organism was also cross resistant to domiphen bromide and alkyldimethyl 3,4-dichlorobenzylammonium chloride. In this study the concentration of domiphen bromide utilized (50 μg/mL (1:20,000)) is equivalent to that contained in commercially available domiphen bromide mouthwashes. However, exposure time to this concentration was 10 days, a period of time which would not be achieved with a mouthwash.

None of the clinical studies supplied by a manufacturer as a Panel submission provide acceptable evidence for the effectiveness of domiphen bromide (Ref. 23).

Further studies by Wyler, Miller, and Micik (Ref. 24), Jaconia and Eisman (Ref. 25) and Weerts and Eisman (Ref. 26) did not use domiphen bromide as a single ingredient and therefore do not support the effectiveness of domiphen bromide.

Domiphen bromide manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data available from controlled studies to establish the effectiveness of domiphen bromide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older. Use a 0.005-percent concentration of domiphen bromide in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 455, 1976.

(2) Lawrence, C. A., and S. S. Block, "Quaternary Ammonium Surface-Active Disinfectants," *in* "Disinfectants, Sterilization, and Preservation," Lea and Febiger, Philadelphia, pp. 438–452, 1968.

(3) Kutscher, A. H., and J. Budowsky, "Observations on the Clinical Use of Bradosol," *Oral Surgery, Oral Medicine, and Oral Pathology,* 7:873–875, 1954.

(4) Halpern, L. and R. Weiss, Draft of unpublished study sponsored by Ciba-Geigy Pharmaceutical Co., 1949, in OTC Volume 130049.

(5) Foster B. Snell, Inc., Report to Ciba-Geigy Pharmaceutical Co., 1971 in OTC Volume 130049.

(6) OTC Volume 130049.

(7) Barrett, W. E., et al., "Toxicity of a New Antiseptic (betaphenoxy-ethyl-dimethyl dodecyl ammonium bromide) (PDDB)," *Federation Proceedings,* 6:307–308, 1947.

(8) D'Arcy, P. F., and E. P. Taylor, "Quaternary Ammonium Compounds in Medicinal Chemistry: I," *Journal of Pharmacy and Pharmacology,* 14:129–146, 1962.

(9) Hays, H. W., et al., "Some Pharmacologic Effects of an Antiseptic, betaphenoxy-ethyl-dimethyl dodecyl ammonium bromide (PDDB)," *Federation Proceedings,* 6:337, 1947.

(10) OTC Volume 130049.

(11) Sturzenberger, O. P., and G. J. Leonard, "The Effect of a Mouthwash as Adjunct in Tooth Cleaning," *Journal of Periodontology,* 40:299–301, 1969.

(12) Gjermo, P., K. L. Baastad, and G. Rolla, "The Plaque-Inhibiting Capacity of 11 Antibacterial Compounds," *Journal of Periodontal Research,* 5:102–109, 1970.

(13) Shern, R., K. W. Swing, and J. J. Crawford, "Prevention of Plaque Formation by Organic Fluorides," *Journal of Oral Medicine,* 25:93–97, 1970.

(14) McCabe, R. M., P. H. Keyes, and A. Howell, Jr., "An In Vitro Method for Assessing the Plaque Forming Ability of Oral Bacteria," *Archives of Oral Biology,* 12:1653–1656, 1967.

(15) Turesky, S., I. Glickman, and R. Sandberg, "In Vitro Chemical Inhibition of Plaque Formation," *Journal of Periodontology,* 43:263–269, 1972.

(16) Seidenberg, S., "Bakteriologische Beurteilung eines neuen Desinfektronsmittels aus der Reihe der quaternaren Ammoniumverbindungen (Bradosol)," *Schweizerische Medizinische Wochenschrift,* 79:978–980, 1949.

(17) Kutscher, A. H., et al., "Growth Inhibiting Properties of Phenoxy-ethyl-dimethyl-dodecyl-ammonium bromide (PDDB) (Bradosol) Against *Candida albicans* in Vitro—Preliminary Report," *Antibiotics and Chemotherapy,* 4:1045–1049, 1954.

(18) Scala, C., and F. Vicari, "Antibiotici e Composti Ammonic-Quaternari: Ricerche in Vitro Sugli Effetti Dell'associazione Acromicina-Bradosol Sullo Stafilococcus aureus e Sul B. coli," *Rivista Patologia Clinica,* 10:685–694, 1955.

(19) Bavin, E. M., E. Kay, and D. Simmonite, "Some Observations on the Activity of Mixtures of Antibacterial Substances," *Journal of Pharmacy and Pharmacology,* 7:676–682, 1955.

(20) Kutscher, A. H., et al., "Fungicidal Properties of Phenoxy-ethyl-dimethyl-dodecyl-ammonium Bromide (PDDB) Against *Candida albicans* in vitro: II," *Antibiotics and Chemotherapy,* 6:400–403, 1956.

(21) Knusel, F., and P. Loustalot, "Zur Chemotherapie der Zahnkaries," *Schweizerische Monatsschrift Zahnheilk,* 75:168–180, 1965.

(22) Adair, F. W., S. G. Geftic, and J. Gelzer, "Resistance of *Pseudomonas* to Quaternary Ammonium Compounds: II. Cross-Resistance Characteristics of a Mutant of *Pseudomonas aeruginosa,*" *Applied Microbiology,* 21:1058–1063, 1971.

(23) OTC Volume 130050.

(24) Wyler, D., R. L. Miller, and R. E. Micik, "Efficacy of Self-Administered Preoperative Oral Hygiene Procedures in Reducing the Concentration of Bacteria in Aerosols Generated During Dental Procedures," *Journal of Dental Research,* 50:509, 1971.

(25) Jaconia, D., and P. C. Eisman, unpublished study conducted by Ciba Pharmaceutical Co., in OTC Volume 130050.

(26) Weerts, J., and P. S. Eisman, unpublished study conducted by Ciba Pharmaceutical Co., in OTC VOlume 130050.

j. *Ethyl alcohol.* The Panel concludes that ethyl alcohol is safe but that there are insufficient data available to permit final classification of its effectiveness as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

Chemically, ethyl alcohol is ethane with one hydrogen replaced by a hydroxyl group (C_2H_5OH) (Ref. 1). It is also known as hydroxyethane, ethanol, ethyl hydroxide, rectified spirit, spirits or wine, and by various other names. Pure alcohol contains not less than 92.3 to 93.8 percent by weight and 94.9 to 96 percent by volume of ethanol at 15.56° C, the remainder being water (Ref. 2). Alcohol has been made for many centuries by fermentation of various carbohydrates by yeast. Alcohol may also be produced synthetically by hydration of ethylene, which is available in abundance in natural gas and coke oven gases. Another synthetic method utilizes acetylene which is catalytically hydrated to acetaldehyde and then hydrogenated again, aided by a catalyst, to ethyl alcohol.

The term "proof spirit," as used in the United States, refers to a produce containing 50 percent by volume of alcohol. Fifty percent alcohol is sometimes designated as 100 proof. The strength of any solution of ethyl alcohol may be expressed in proof by multiplying the concentration of C_2H_5OH by volume by two.

Alcohol is very hygroscopic, and concentrations above 95 percent must be made by special processing. The 95 percent alcohol boils at 78.2° C; the anhydrous alcohol boils at 78.3° C. It is not possible to obtain anhydrous alcohol (absolute alcohol) by direct distillation, since alcohol represents a constant boiling mixture of ethanol and water at 78.2° C. Absolute or "water-free" alcohol may be made by adding chemicals, such as anhydrous copper sulfate or calcium sulfate, which form hydrates and remove the water after which the alcohol is purified by distillation (Ref. 3).

Alcohol is a transparent, colorless, mobile, volatile liquid with a characteristic, somewhat pungent, odor and a burning taste. Alcohol is flammable. Alcohol is miscible with water in all proportions. It is also miscible with ether and chloroform. The specific gravity is not more than 0.816 at 15.56° C (Ref. 2).

The U.S. government has established regulations authorizing the addition of substances to alcohol which render it unfit for beverage purposes although suitable for industrial use. These various liquids are referred to as "denatured alcohols."

Diluted alcohol is a mixture of equal volumes of alcohol and purified water. This mixture contains between 41 and 42 percent by weight (48.4 to 49.5 percent by volume) of C_2H_5OH. When alcohol is mixed with water, a contraction in volume occurs. The specific gravity of diluted alcohol is between 0.935 and 0.937 at 15.5° C. Diluted alcohol is used mainly as a solvent for various pharmaceutical purposes. Concentrations up to 35 percent are used in certain mouthwashes. Higher concentrations cause burning of the mucous membranes. Rubbing alcohol consists of 68,5 to 71.5 percent by volume of absolute ethyl alcohol combined with a denaturant.

(1) *Safety.* The Panel concludes that ethyl alcohol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The safety of alcohol has been established through long-term use. Alcohol is a central nervous system depressant and produces coma analagous to other depressant drugs if overdosage occurs. Extensive studies indicate that there is a correlation between the concentration of alcohol in blood, urine, or expired air and the concentration on the nervous system. Alcohol is absorbed rapidly from the gastrointestinal tract when ingested in pure form or from alcoholic beverages. About 20 percent of orally ingested alcohol is absorbed by the stomach and the remainder by the intestines. The quantity absorbed from the mouth and throat is not significant. The rate of absorption is altered by the presence or absence of food in the stomach as well as the type of food present. Protein and fat delay absorption. The alcohol diffuses easily and rapidly into the tissues. The concentration in the tissues is related to the concentration of water present in the extracellular and intracellular compartments (Ref. 4).

From 90 to 98 percent of ingested alcohol is metabolized by oxidation in the liver. Acetaldehyde forms first, then acetic acid, and ultimately CO_2 and water (Ref. 5). Unmetabolized portions are excreted chiefly in the urine and to an insignificant degree in expired air. In expired air the concentration is approximately one two-thousandths of that of the arterial blood. In an obviously intoxicated person the urine may contain as much as 5 g/L; while at the same time the expired air contains only a few mg/L. Only traces are found in sweat, milk, and bile.

The effect of alcohol on the heart and circulation is not marked. Blood pressure and cardiac output may be slightly increased after ingestion of moderate amounts of alcohol. In moderate doses alcohol causes peripheral vasodilatation. A feeling of warmth and flushing of the skin is experienced. The vasodilation probably results from the central vasomotor depression (Ref. 4).

Alcohol has a marked influence on the gastric and intestinal digestion. Dilute alcohol solutions stimulate gastric secretions. Fifteen milliliters of 7 percent alcohol has been used as a test meal to promote secretion of hydrochloric acid. Accumulation of fat in the liver in normal individuals follows the ingestion of relatively small amounts of alcohol. This response to alcohol is acknowledged by some workers to be extremely valuable as a protective mechanism. Alcohol increases the rate of synthesis of fat by the liver slices. Apparently this is caused because of the increase of the ratio of reduced nicotinamide-adenine-dinucleotide ($NADH_2$) to non-reduced dinucleotide (NAD).

The local action of alcohol is mildly irritant, feeble, very slightly anesthetic, distinctly germicidal, and astringent. Alcohol has a marked potential for abuse, and for this reason the quantity used as a solvent in oral health care products is limited to 35 percent.

The symptoms of acute alcohol poisoning are widely known and a detailed description is unnecessary in a discussion of this type. However, it must be emphasized that there is a similarity between the symptoms of alcohol overdose and injuries and diseases that induce coma. Furthermore, alcohol acts additively with narcotics, hypnotics, and other central nervous system depressants that likewise cause coma.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of ethyl alcohol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

Alcohol, in concentrations of less than 70 percent, is ineffective as an antimicrobial agent for use in medicine. Alcohol is widely used for application to the skin as an antimicrobial agent. Alcohol acts as an irritant, anhidrotic, and as an astringent by virtue of its ability to precipitate cellular protein. Thus, it is useful in the hygienic care of the skin in bedridden patients for the prevention of ulcers. Its cooling quality when it evaporates is well known. Alcohol may be used to remove phenol, poison ivy, etc. from the skin. Alcohol is a neurolytic agent and has been used for injection into nerves for relief of intractable pain. Alcohol has also been used to treat intractable pruritus. Intravenous alcohol has been reported to be effective as an anesthetic and basal narcotic, but the margin of safety is too narrow, and it is not used for this purpose. When taken internally, alcohol tends to increase sweating by dilating

the vessels of the skin. For this reason it is frequently used as a diaphoretic in mild infections, such as coryza. A 3-percent solution has been used for inhalation as an antifoaming agent in pulmonary edema.

Alcohol kills microorganisms by denaturing and precipitating proteins. It had been assumed that 95 percent ethyl alcohol is superior in its ability to kill bacteria on the skin. It is now well-established that 70 percent alcohol is more effective because 95 percent alcohol coagulates the cytoplasm on the periphery of the cell, and, therefore, is unable to penetrate into the cell. Most bacterial spores are resistant to alcohol (Ref. 6).

Concentrations that kill bacteria cause burining and intense discomfort and are too irritating when applied to ulcerations and inflammatory lesions on the mucuous membranes of the mouth and throat.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of alcohol as an antimicrobial agent for the treatment of symptons such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel recommends no dose for alcohol because it is used as a solvent for other active ingredients that possess antimicrobial activity and such combinations may act in consort with alcohol at doses below 70 percent of the effective antimicrobial dose.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B. 3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 31, 1976.

(2) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1252–1254, 1975.

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 38–39, and 43, 1973.

(4) Modell, W., H. O. Schild, and A. Wilson, "Applied Pharmacology," American Ed., W. B. Saunders Co., Philadelphia, pp. 859–867, 1976.

(5) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 851–873, 1957.

(6) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 884–885, 1977.

k. *Eucalypto.*. The Panel concludes that eucalyptol is safe, but that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Eucalyptus oil is a volatile oil obtained from the fresh leaves of *Eucalyptus globus.* It is also a constituent of that body of miscellaneous terpenes and other organic compounds obtained from plants referred to as the "volatile oils." Eucalyptus oil and its active ingredient eucalyptol have been described elsewhere in this document. (See part III. paragraph B.3.a. above—Eucalyptol, also part IV, paragraph A.9 above—Volatile oils.)

(1) *Safety.* The safety of eucalyptol has been described elsewhere in this document. (See part III. paragraph B.3.a.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of eucalyptol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are no data from controlled studies that establish eucalyptol or eucalyptus oil as an effective antimicrobial agent.

"The Merck Index" (Ref. 1) categorizes oil of eucalyptus as an expectorant, anthelmintic, and local anesthetic. Eucalyptol has been described in "United States Pharmacopeia" which states that it is used in dentistry as an antiseptic mouthwash. Eucalyptol is a mild irritant to the mucous membranes. Eucalyptol is considered a constituent of the volatile oils, and traditionally the volatile oils have been considered to have antimicrobial activity in the mouth and throat. The volatile oils have been discussed elsewhere in this document. (See part IV. paragraph A.9. above—Volatile oils.)

The Panel finds no data on eucalyptol's mode of action, spectrum of antimicrobial activity, conditions in which it acts topically, in vivo speed of antimicrobial activity, or under which conditions this occurs.

The Panel reviewed a submission in which a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested for antimicrobial activity (Ref. 2). It was allegedly found that eucalyptol possessed antimicrobial activity. The testing was not performed using the individual ingredient but by removing the eucalyptol from the mixture and determining the effectiveness of the mixture when eucalyptol was not present. The mixture, minus eucalyptol, exhibited less antimicrobial activity than when the eucalyptol was present. The Panel does not consider these data to be proof of the effectiveness of eucalyptol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of eucalyptol as and antimicrobial agent for treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.025-percent concentration of eucalyptol in the form of a rinse, mouthwash, or gargle not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervison of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 882–883, 1976.

(2) OTC Volume 130136.

1. *Gentian violet.* The Panel concludes that gentian violet is safe, but that there are insufficient data available to permit final classification of the effectiveness of gentian violet as an OTC antimicrobial active ingredient for topical use on the mucous membranes of

the mouth and throat when used within the proposed dosage limit set forth below.

Gentian violet is one of the triphenylamine (rosanaline) dyes which are derivatives of triphenylmethane. It is a mixture of several dyes, the most abundant of which is hexamethylpararosaniline chloride (Ref. 1). In addition, it contains pentamethylpararosaniline chloride and tetramethylpararosaniline chloride (Ref. 2). Chemically gentian violet must be considered a mixture of substances. Other related dyes are crystal violet and methyl violet. However, these are not absolutely identical to gentian violet, differing both in the specific methylrosaniline derivative present and in its proportions. Gentian violet is also known as aniline violet and crystal violet.

Gentian violet is a dark green powder, a crystallin mixture consisting of greenish pieces with a metallic luster, which is practically odorless. Gentian violet is soluble in water and chloroform and partially insoluble in ether. One gram dissolves in about 10 mL alcohol and approximately 15 mL glycerol (Ref. 2).

Synthetic organic dyes have been used for many years as antimicrobial agents, acting against bacteria, fungi, and protozoa. However, they have been supplanted by more effective and dependable antimicrobial agents and enjoy only limited use in treating infections. They have often been used for treating wounds. The antiseptic dyes have a marked specificity of action and each type of dye differs in its specificity. This specificity is dependent upon the staining properties of each type of bacteria. The staining properties of bacteria are largely dependent upon the physiochemical characterisitics of the constituents of the protoplasm of bacterial cells.

Antiseptic dyes fall into two groups, depending upon whether the chromogenic radical is electropositive or electronegative in the endoplasm and nucleus. The electropositive dyes have a special affinity for gram-positive organisms. They are also more active in a basic medium and, therefore, are called basic dyes. This does not mean that compounds themselves are basic, but rather that they have an affinity for chemically basic groups located in microbial cells. The acid dyes are active against gram-negative organisms and act best in an acid medium. Other factors such as species of organism, pH, concentration, and penetrability of the cell membrane also influence the activity of germicidal dyes. The antiseptic properties of dyes are greatly diminished in the presence of serum other other organic material Temperatures higher than that of the body also decrease their effectiveness.

The triphenylmethane or rosaniline dyes are basic dyes that have antiseptic properties and are effective against gram-positive organisms. The group includes, in addition to gentian violet, crystal violet, methyl violet, brilliant green, and acid and basic fuchsin. The first four are used medicinally.

Gentian violet and related dyes are particularly effective against staphylococcus. *Corynesbacterium diphtheriae,* and *Streptococcus pyogenes.* They are also effective against the causative organism of Vincent's angina, the various strains of candida, torula, epidermophyton, and trichophyton. Gram-negative bacteria are resistant to the rosaniline dyes. Rosaniline dyes form a precipitate with necrotic tissue. This property was once considered of unique value in the treatment of burns, but is not utilized in current therapeutics (Ref. 3).

The Panel reviewed one submission for a marketed product that contained labeling information but no data on the safety or effectiveness of gentian violet (Ref. 4).

(1) *Safety.* The Panel concludes that gentian violet is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Gentian violet is an antibacterial, antifungal, and anthelmintic dye. The oral LD_{50} in mice and rats is 1.2 to 10 g/kg. Locally, when applied to the mucous membranes and skin, gentian violet is nontoxic. When ingested it may cause nausea, vomiting, diarrhea, and lassitude. Intravenous injection of impure preparations may produce a servere shock-like reaction.

Gentian violet has been used by the oral route as an anthelmintic because it is active against *Oxyuris vermicularis* (pinworm). Pinworm infection was once treated by giving 50 mg in enteric-coated tablets which had a 4-hour disintegration time, three times a day before meals for 8 to 10 days. Children were given 5 to 10 mg a day for each year of age in divided doses. After an interval of a week, the course was repeated.

Severe heart, kidney, or liver disease are considered to be contraindications to the use of the dye internally. Slough of the mucous membranes of the mouth has been reported in children when gentian violet was used as an anthelmintic dye.

(2) *Effectiveness.* The Panel concludes that there are insufficient data to permit the final clasification of the effectiveness of gentian violet as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed limits set forth below.

Gentian violet is bactericidal to gram-positive organisms, particularly staphylocci, *Corynebacterium diphtheriae,* and *Pseudomonas pyocyanea.* Gram-negative bacteria and tubercle bacilli are not affected by gentian violet. Gentian violet inhibits the growth of the spirochete that causes Vincent's angina as well as the growth of fungi such as candida, torula, epidermophyton, and trichophyton.

Gentian violet forms precipitates with necrotic tissue, and this property was formerly used in treatment of burns. Gentian violet is used in aqueous solutions to treat lesions of the skin and mucous membranes in which gram-positive bacteria are the causative pathogen. These lesions require identification by a physician and are not amenable to self-diagnosis and treatment.

Topical application of a 1-percent solution is effective in the treatment of infections due to *Candida albicans,* otherwise known as thrush. Diagnosis and treatment of thrush requires the services of a physician or dentist.

For the most part gentian violet has been replaced by more effective substances. It stains certain dental restorations and the oral tissues and is no longer used in the treatment of oral infections.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of gentian violet as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Swab affected area with a 1.0-percent solution of gentian violet not more than two to three times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist of physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral healt care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth

below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 557–558, 1973.

(2) "United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 219, 1975.

(3) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol, et al., Mack Publishing Co., Easton, PA, p. 1091, 1975.

(4) OTC Volume 130051.

m. *Hydrogen peroxide.* The Panel concludes that hydrogen peroxide is safe, but that there are insufficient data available to permit final classification of the effectiveness of hydrogen peroxide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Synonyms for hydrogen peroxide (H_2O_2) are hydrogen dioxide and hydroperoxide (Ref. 1). Hydrogen peroxide is a colorless, rather unstable liquid with a bitter taste, and it is caustic to the skin. It is miscible with water, soluble in ether, and insoluble in petroleum ether. Hydrogen peroxide is decomposed by many organic solvents. Solutions of hydrogen peroxide gradually deteriorate and are usually stabilized by the addition of acetanilide or similar organic materials (Ref. 1).

Hydrogen peroxide solution 3 percent, also known as hydrogen dioxide solution or oxydol, contains 2.5 to 3.5 percent by weight of H_2O_2 which is equal to 8 to 12 volumes of oxygen. It is classified as a topical anti-infective (Ref. 1). This concentration has been widely used as a cleansing and topical antiseptic agent for suppurative wounds and inflammation of the skin and the mucous membranes. The dental profession also uses it for irrigation during root canal therapy and as a mouth rinse for acute necrotizing gingivitis. The unpleasant taste of hydrogen peroxide has been suggested to be due to the acetanilide (Ref. 2).

The 30-percent solution of hydrogen peroxide (superoxol) is a strong oxidizing agent that has been used for bleaching of vital and pulpless teeth. The soft tissues of the mouth should be protected against its irritant action by the use of a rubber dam.

The decomposition of hydrogen peroxide can be hastened by the action of enzymes, such as catalase (hydrogen peroxide oxidoreductase), peroxidases, reduced nicotinamide adenine dinucleotide phosphate (NADP), and cytochrome c.

In the decomposition of hydrogen peroxide, one molecule releases one atom of oxygen which combines with a substrate that is oxidized.

(1) *Safety.* The Panel concudes that hydrogen peroxide is safe as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

A submission to the Panel on hydrogen peroxide contains no data relating to any aspect of safety (Ref. 3). However, a submission to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Ref. 4) contains a literature review as well as studies with 10 percent hydrogen peroxide contained in proprietary gels.

The comparative oral irritant actions of hydrogen peroxide and sodium perborate, when these substances were used as dentifrices, have been described (Ref. 5). Sodium perborate was found to be the more irritating, although hydrogen peroxide also produced noticeable changes,such as edema and ulceration of the mucous membranes of the gingival and lingual areas. Hydrogen peroxide should not be used as a mouthwash for long periods of time. The acidity of even diluted solutions of hydrogen peroxide will result in the decalcification of tooth substance. Continued long use may also result in the development of a black hairy tongue (Ref. 6).

Relatively little information has been found in the literature regarding the acute toxicity of hydrogen peroxide, but it appears to be low. Spector (Ref. 7) states that the approximate LD_{50} for rats is 21 mg/kg if given intravenously and 700 mg/kg when applied cutaneously. Gosselin et al. (Ref. 8) also indicate a low toxicity. They comment that there are no primary effects when hydrogen peroxide is ingested because it is decomposed in the bowel before absorption. However, decomposition is associated with the release of large volumes of oxygen, a volume of oxygen equal to 10 times the volume of the solution, and esophagitis and gastritis may occur. Rupture of the colon, proctitis, and ulcerative colitis have been reported to follow hydrogen peroxide enemas.

There are studies (Ref. 4) that estimate that the LD_{50} of 10 percent hydrogen peroxide contained in various gels that were adminstered orally in six rats is over 5 g/kg. No controls were used, so the possible inactivation of peroxide toxicity by the gels is uncertain. No irritation of the stomach mucosa was observed in the rats receiving 10 percent hydrogen peroxide in gels, although only 2 rats were sacrificed. The same studies indicated that 0.2 mL of the test gels were only transiently irritating in hamster cheek pouches in 24 animals or guinea pig gingiva in 6 animals.

Martin et al. (Ref. 9) studied the irritant effect of hydrogen peroxide on the gingiva of anesthetized dogs by applying a 1-percent solution via a continuous drip onto a cotton pledget at the rate of 15 mL/hr. The number of animals used was not stated. Edema resulted which was followed by complete destruction and sloughing of the cornified layer of the epithelial cells. Other histological changes were also noted.

In a similar study, Dorman and Bishop (Ref. 10) applied 1.2 percent hydrogen peroxide by continuous drip to tongues of 10 anesthetized dogs. Edema invariably occurred within 30 minutes, reaching a peak in 3 to 4 hours.

In a study of the possible anticariogenic effects of 0.5 percent to 1.5 percent hydrogen peroxide added to the drinking water of rats, Shapiro, Brat, and Ershoff (Ref. 11) noted that growth, as determined by body weight, was retarded over an 8-week period as compared to the controls. However, the control animals were neither pair-fed nor pair-watered so this observation is not conclusive. Lisanti and Eichel (Ref. 12) also noted a weight reduction in hamsters receiving 3 percent hydrogen peroxide in the drinking water for 55 days, but there again pair-feeding and pair-watering were not done.

Eighty-eight dental students self-administered a 6- to 12.5-percent hydrogen peroxide solution (Ref. 4). They used it as a mouthwash or dipped their toothbrushes into the solution before brushing their teeth. Application of the hydrogen peroxide was 2 to 3 times per day for a period ranging from 1 to 2.5 months. Some gingival changes were noted (6.4 percent "redder," 3.4 percent "paler") and 6.8 percent of the group developed hyperkeratinized filiform papillae of the tongue. Black hairy tongue, which seems to be associated mainly with prolonged usage of carbamide peroxide and sodium perborate (Ref. 13), was not observed.

Biopsies of the attached interdental epithelium of 30 male patients were made after topical application with 30 percent hydrogen peroxide (Ref. 14). The peroxide was applied three times per week for 4 weeks to the interdental papilla. Applications were for 1 minute, followed by irrigation with water. The mitotic index was increased 5 to 8 fold.

However, single applications of hydrogen peroxide has the effect of a prolongation of mitosis suggesting that the increased rate of mitosis was more apparent than real.

In a study by Orban (Ref. 15), the application of 30 percent hydrogen peroxide twice weekly for 3 to 6 weeks was reported to result in significant changes in the epithelium and connective tissues of chronically inflamed gingival tissue. The basal cell layer became considerably thicker, an increase in mitosis was noticed, and irregular rete pegs penetrated deeply into the connective tissue. Proliferation of the connective tissue took place, and hyperkeratosis of the epithelium was observed. The author interpreted these changes as beneficial for healing. No mention was made of the number or age of the subjects used, the exact site of application of the agent (although application to the free gingiva is shown in a photograph), the method of application, or the duration of application.

One reference, without referring to any experimental data, stated "hypochlorite or peroxide solutions at concentrations above 7 percent may be regarded as toxic to soft tissue, and hence must be used prudently" (Ref. 16).

Knighton (Ref. 17), however, states that hydrogen peroxide should not be used on newly granulating surfaces because it tends to break down the new, delicate tissue growth.

The Panel concludes that concentrations up to 3 percent of hydrogen peroxide are safe for OTC use on the mucous membranes of the mouth and throat.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of hydrogen peroxide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Most bacteria are relatively resistant to the action of peroxides. This relative resistance may be the result, in part, of the bacterial production of the enzyme catalase that is present in some cytochrome-containing aerobic and facultative anaerobic bacteria. Some anaerobic bacteria that lacks catalase produce peroxidase enzymes in lieu of the catalase. Both catalases and peroxidases are listed under the general enzyme classification "hydroperoxidases."

Hydrogen peroxide, if allowed to reach a high concentration, is toxic to bacteria in vitro. However, the concentration of the "hydroperoxidases" either by the bacteria themselves or by the tissues in vivo prevents the accumulation of this large threshold concentration.

Catalase has two activities. It decomposes hydrogen peroxide, and it oxidizes secondary substrates. Catalase activity is present in nearly all human organs and cells. The liver and kidney and the erythrocytes are rich in catalases. Oral tissues also have tissue catalases. The tissue catalases function in the same manner as microbial catalases, i.e., they prevent the accumulation of noxious H_2O_2.

Human leukocytes and erythrocytes produce peroxidases. The saliva contains salivary peroxidases. The mechanism of action of these peroxidases is similar to the action of the catalases. The released oxygen combines with a substrate to form another compound and no gas is evolved.

One molecule of catalase can deompose 44,000 molecules of hydrogen peroxide per second. This indicates that a minute amount of enzyme is able to decompose a large amount of peroxide.

It was long thought that the activity and growth of obligate anaerobes were inhibited or killed by hydrogen peroxide because they lack the catalase possessed by some aerobes, e.g., *Staphylococcus aureus.* However, aerobes and facultative anaerobes, which lack catalase, are not necessary killed by H_2O_2. Recent findings suggest that a highly reactive and very toxic superoxide formed by flavoenzymes inhibits anaerobes because they do not produce the superoxide dimutase produced by aerobes.

Alternatively, the maintenance of certain essential enzymes in an oxidized state may prevent some anaerobes from multiplying because oxygen prevents flavoproteins from functioning (Ref. 18). The potential activity of H_2O_2 is, therefore, complex and requires a knowledge of the metabolic pathways of the specific susceptible or resistant microorganisms.

In one clinical study (Ref. 19), 0.3 percent hydrogen peroxide was compared with 0.3 percent sodium peroxyborate in reducing the severity of acute necrotizing ulcerative gingivitis. Twenty-five patients were used in each group during a double-blind trial. As judged by clinical observation and patient response, both compounds were found to be effective with no statistically significant differences between the two compounds. However, since this study utilized no control, the efficacy could have been due to a mechanical effect which might be obtained by rinsing with saline solution or water.

Another study, although not designed to directly evaluate the clinical effectiveness of hydrogen peroxide, contains data which should be noted. In this study, which was designed to evaluate antiseptic activity, six subjects rinsed their mouths for 1 minute twice daily over a 5-day period with 0.5 percent hydrogen peroxide suspended in 33 percent glycerin. No irritation of the oral mucosa was noted, but when 0.75 percent hydrogen peroxide in 50 percent glycerin was used "certain subjects noted irritation of the mouth and gums as evidenced by chapping and loss of taste." No explanation for this observation is offered, but it seems probable that these effects could have been due to the humectant effect of the 50-percent glycerin rather than the 0.75-percent hydrogen peroxide (Ref. 20).

A further reference suggests that hydrogen peroxide "is one of the better agents" to discourage new tissue proliferation and promote epithelialization over the newly formed tissue (Ref. 16). The application, which is not described, was intended to be used after periodontal surgery. No substantiating data are presented.

Many bacteriological studies have been performed with more stable forms of hydrogen peroxide, such as carbamide peroxide in glycerin, but relatively few with hydrogen peroxide alone. Concentrations as low as 0.1 to 0.25 percent are said to kill *Escherichia coli* and *Staphylococcus aureus* in 1 hour, but in 5 minutes. Obviously, the 1-hour in vitro exposure time is unlikely to occur in vivo because of the rapid decomposition by tissue and salivary catalase and by tissue peroxidase. In fact, most of the early reports, circa 1940 to 1950, on the bacterial activity of hydrogen peroxide in vitro failed to take into account the conditions which exist in vivo and include rapid breakdown in the presence of tissue, blood, and saliva. It is difficult to imagine circumstances whereby hydrogen peroxide kills bacteria, but is not injurious to tissue.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of hydrogen peroxide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use hydrogen peroxide in concentrations up to 3 percent. For children under 3 years of age, there is no recommended dosage except the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial

active ingredients. (See part IV. paragraph B.2. above—Categroy I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 633, 1976.

(2) Shapiro, M., "Dental Pharmacology," *in* "The Scientific Bases of Dentistry," edited by H. M. Myers, W. B. Saunders Co., Philadelphia, pp, 295–297, 1966.

(3) OTV Volume 130060.

(4) OTC Volume 080050.

(5) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 12th Ed., C. V. Mosby Co., St. Louis, p. 427, 1961.

(6) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 314, 1977.

(7) Spector, W., "Handbook of Toxicology: Volume I," W. B. Saunders Co., Philadelphia, p. 160, 1956.

(8) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 76, 1976.

(9) Martin, J. H., et al., "Cellular Response of Gingiva to Prolonged Application of Dilute Hydrogran Peroxide," *Periodontics,* 39:208–210, 1968.

(10) Dorman, H. L., and J. G. Bishop, "Production of Experimental Edema in Dog Tongue with Dilute Hydrogen Peroxide," *Oral Surgery Oral Medicine and Oral Pathology,* 29:38–43, 1970.

(11) Shapiro, M., V. Brat, and B. H. Ershoff, "Induction of Dental Caries and Pathological Changes in Periodontium of Rat with Hydrogen Peroxide and Other Oxidizing Agents," *Journal of Dental Research,* 39:332–343, 1960.

(12) Lisanti, V. F., and B. Eichel, "Antioxidant Inhibition of Experimentally Induced Caries in Hamsters," *Journal of Dental Research,* 42:1030–1035, 1963.

(13) Miller, S. C., et al., "Hydrogen Peroxide and Sodium Perborate: Their Comparative Oral Irritant Action," *Journal of the American Dental Association,* 25:1957–1973, 1938.

(14) Gargiulo, A. W., "Biologic Effect of Hydrogen Peroxide Upon the Human Gingiva," *Periodontics,* 1:199–203, 1963.

(15) Orban, B., "Action of Oxygen on Chronically Inflamed Gingival Tissue," *Journal of the American Dental Association, 29:2018–2025, 1942.*

(16) Gurney, B. F., "Oxygen Therapy: Part Two," *Dental Digest,* 74:400–401, 1968.

(17) Knighton, H. T., "The Effect of Oxidizing Agents on Certain Non-Spore-Forming Anaerobes," *Journal of Dental Research,* 19:429–439, 1940.

(18) Davis, B. D., et al., "Microbiology," 2d Ed., Harper and Row, Hagerstown, MD, pp. 48–49, 1973.

(19) Wade, A. B., and K. B. Mirza, "The Relative Effectiveness of Sodium Peroxyborate and Hydrogen Peroxide in Treating Acute Ulcerative Gingivitis," *Dental Practitioner and Dental Record,* 14: 185–187, 1964.

(20) Slanetz, L. W., and E. A. Brown, "Studies on the Numbers of Bacteria in the Mouth and Their Reduction by the Use of Oral Antiseptics," *Journal of Dental Research,* 28:313–323, 1949.

n. *Iodine.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of iodine as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Iodine is an element, being one of the four halogens. All four halogens are oxidizing agents. Its moleculer is diatomic (I_2). It was first discovered in 1811 by Courtois (Ref. 1). Iodine is obtained from seaweed and certain algae, in sea water, brine, oil field brines, and from Chilean saltpeter. Elemental iodine consists of bluish-black scales or plates with a metallic luster (Ref. 2). It sublimes, giving off a violet vapor which is corrosive. Iodine melts at 113° C, but is volatile at ordinary room temperature. One gram dissolves in 2,950 mL water, 12.5 mL alcohol, 10 mL benzene, 50 mL carbon tetrachloride, and 80 mL glycerin. It is freely soluble in solutions of water-soluble iodides, such as those of sodium and potassium, and in mixtures of alcohols and aqueous iodides. These hydroalcoholic solutions are used as germicides and belong to a group of iodinated compounds called "iodophors."

Iodine is incompatible with oil of turpentine, starch, tannin, alkalis, alkaloids, and metallic salts.

Iodine is an essential element found in plant foods. Animals used for food that feed on plants containing iodine are also a source of the element. Iodine deficiency results in goiter. The minimal daily requirement of iodine has been estimated to be 100 μg in terms of elemental iodine. Iodine was first used therapeutically in 1819 for the treatment of goiter. Iodine preparations have been listed in the "United States Pharmacopeia" since 1840.

The acceptable composition for tincture of iodine is not less than 1.8 g and not more than 2.2 g of iodine, and not less than 2.1 g and not more than 2.6 g of sodium iodide in each 100 mL of 44 to 50 percent ethyl alcohol or an appropriate denatured alcohol.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Elemental iodine has local irritant and germicidal actions (Ref. 1). It has been used as a counterirritant in various forms of arthritis, particularly those due to trauma. Solutions of elemental iodine have been a frequent cause of poisioning. The symptoms of acute toxic reactions are pain in the epigastrium followed by nausea and vomiting. The vomitus may be brown or blue if there has been any starch in the stomach and later may become bloody. Excessive thirst, abdominal cramps, and circulatory failure may follow in severe cases. The most efficient antidote is a solution of sodium thiosulfate. When this is not available, several tablespoonsful of cornstarch stirred with water may be used. In its absence, bread or other starchy materials may be ingested (Ref. 3).

Iodine or iodine derivatives, such as sodium or potassium iodine, and organic compounds containing iodine which are given continuously over long periods of time, even in medicinal doses, give rise to a more or less serious type of chronic toxicity known as iodism. This is usually characterized by pain or heaviness in the region of the frontal sinuses. In some instances, soreness of the mucous membrane of the mouth and throat results. Skin lesions of all degrees of severity have followed internal use of iodides in sensitive persons. Absorption of iodides has caused the shrinkage of the breasts in the famale and atrophy of the testicles in the male. The protracted use of iodides may cause parotitis apparently due to plugging of the ducts of the salivary glands by dead or injured cells. In some instances, sensitivity to iodides may be responsible for vasculitis and polyarteritis.

Gleason et al. (Ref. 4) rate the toxicity of elemental iodine as 5 (extremely toxic, with a probable lethal dose of 5 to 50 mg/kg). A study of attempted suicides associated with iodine ingestion indicates that the lethal range is from a few tenths of a gram to more than 20 g (Ref. 5). The probable mean lethal dose is between 2 and 4 g of free elemental iodine. Poisoning is mainly due to its oxidizing and the corrosive action on the gastrointestinal tract. Povidone-iodine is less toxic than the iodine and other iodophors.

Iodine produces a mahogany stain when applied to the skin. Smarting, erythematous inflammation, infiltration of subcutaneous tissue, desquamation of the epidermis into large shreds, and vesication of tissues may result after repeated application.

The effects of iodine on the mucous membranes are even more severe than on the skin and may produce ulceration, corrosion, and sloughing. This action is chemical in nature since it precipitates protein. The protein dissociates the releases iodide so that its action is prolonged, as it is in skin. Iodine is absorbed, somewhat, from the skin and excreted mainly in the urine as the iodide ion. Dilute solutions in non-irritating strength are absorbed from the mucous membranes and are distributed systemically. (See part IV. paragraph B.3.t. below—Povidone-iodine.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Elemental iodine is one of the most potent germicides available. However, its effectiveness as an antimicrobial agent on the mucous membranes of the mouth and throat in the relief of the symptoms of sore throat and sore mouth has not been established.

Iodine has a long history of use as a broad-spectrum antimicrobial agent. It is recognized as having activity against fungi, viruses, and both gram-positive and gram-negative bacteria. The phenol coefficient of iodine may vary between 180 and 237 depending upon the character of the solvent and the species of bacteria tested. It is believed that all microrganisms are killed by the same concentration of iodine, but that various environmental conditions in a wound or on the skin or other surfaces cause changes in the concentration necessary for the killing effect. Albumin decreases the bactericidal action of iodine. In the presence of blood serum a 1:200,000 solution has been bactericidal to staphylococci. Most antiseptics are ineffective aganist tubercle bacilli, but iodine in concentrations as low as 0.0625 percent is bactericidal to human tubercle bacilli in cultures and suspensions. Iodine will kill anthrax spores, but solutions as strong as 7 percent of the tincture must be used, and an exposure of 2 hours is required for such an action.

Iodine is still considered by many to be one of the best wound disinfectants, but it should never be applied in concentrations greater than 2 or 3 percent. Iodine has been and, in some cases, is still used to sterilize the skin prior to surgical procedures. It may be employed in strengths of 5 to 10 percent for this purpose. Iodine is of benefit in the treatment of fungus infections of the skin such as ringworm, foveas, etc. In these conditions, it may be applied as a solution of the tincture (Ref. 6).

Elemental iodine precipitates proteins. The iodine is partly absorbed, partly loosely bound, and partly converted into iodide ions. This precipitation causes persistent irritation, usually short of corrosion. Since the iodine itself is loosely bound, it continues to penetrate into the cells so that the action extends deeply. In the process of acting as an antimicrobial agent, iodine also injures some of the host cells. The effect of this type of injury on wound healing is a matter of concern to the Panel. The iodine is used in the form of tinctures or watery (hydroalcoholic) solutions.

The official tincture contains 3.5 percent iodine and a "strong solution" (Lugol's solution) contains 7 percent iodine in potassium iodide. The potassium iodide makes the tinctures more stable and more miscible with water. Iodine ointments release their iodine slowly so their action is milder and less effective than that of solutions. A part of the iodine is chemically combined with the base in some of the proprietary ointments so that it cannot react with the proteins and is, therefore, ineffective.

The antiseptic action of iodine is used to prepare the skin for operations. A 3-percent alcoholic solution is painted over the dried skin in the operative field on the preceding day and again on the day of the operation. This is preferable to the official tincture since the potassium iodide in the latter delays drying and penetration. Severe irritation may result. The value of iodine for wound disinfection is disputable on the basis that the tissue injury may be more of a detriment and delay wound healing, offsetting the benefits of its antiseptic action. Extensive application to the skin sometimes produces nervous phenomena and fever.

These effects of iodine on the skin and minor wounds are mentioned in detail to emphasize the potency of iodine as an antimicrobial agent and to indicate that it is capable of causing injury to the host cells. The cells of the mucous membranes of the oral cavity are more delicate and are more easily injured by chemical agents than those of the skin. The Panel is concerned about the possible adverse effects of iodine in the mouth and throat. Insufficient data exist concerning such adverse effects particularly for use in rinses and mouthwashes on a daily basis for months at a time.

Iodine manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of iodine as an antimicrobial agent for the treatment of symptoms such as sore throat and sore mouth.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 1.0- to 2.0-percent concentration of iodine in aqueous-alcoholic solutions in the form of a rinse, gargle, spray, or swabbed over the affected area, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Date Required for Evaluation.)

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, "8th Ed., W. B. Saunders Co., Philadelphia, pp. 1117–1120, 1957.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 661–662, 1976.

(3) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, pp. 886–887, 1977.

(4) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section II, p. 82, and section III, pp. 126–128, 1969.

(5) Moore, M., "The Ingestion of Iodine as a Method of Attempted Suicide," *New England Journal of Medicine,* 219:383–388, 1938.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 625–628, 1973.

o. *Menthol.* The Panel concludes that menthol is safe, but that there are insufficient data available to permit final classification of the effectiveness of menthol as an OTC antimicrobial agent for topical use on the mucous

membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Menthol is also known as hexahydrothymol and peppermint camphor (Ref. 1). It is a secondary alcohol obtained from peppermint oil and other mint oils or prepared synthetically by hydrogenation of thymol. Menthol is used as an analgesic, antipruritic, and local stimulant to the mucous membranes and as a counterirritant. The general characteristics of menthol have been described elsewhere in this document. (See part III. paragraph B.1.f. above—Menthol).

(1) *Safety.* The safety of menthol has been described elsewhere in this document. (See part III. paragraph B.l.f. (1) above—Safety).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of menthol as an OTC active antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Menthol is a constituent of certain volatile oils, depending upon the source of the oil. Menthol is lipophilic and, for this reason, has been regarded as an antimicrobial agent. It is actively germicidal, being more powerful than phenol (Ref. 2). Gershenfeld and Miller (Ref. 3) found that even the saturated aqueous solution, which is very dilute, has some antiseptic properties; however, there are no data to indicate the broadness of its spectrum and the degree of its antimicrobial activity. Menthol has been administered orally in the doses of 30 to 120 mg as an interal antiseptic. Menthol is used topically in a 1- to 10-percent solution. Diluted solutions have been used to control superficial infections on the skin.

A submission, in which a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested in vitro for antimicrobial activity, alleges that menthol possesses antimicrobial activity (Ref. 4). The testing was not performed with the individual ingredient alone. The testing was performed by removing menthol from the mixture and determining the effectiveness of the mixture when menthol was absent. Less antimicrobial activity was noted when the menthol was removed. The Panel does not consider this data to be proof of effectiveness of menthol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of menthol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.04- to 2.0-percent concentration of menthol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. Use a lozenge containing 2.0 to 20.0 mg of menthol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 757, 1976.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 697, 1973.

(3) Gershenfeld, L., R. E. Miller, "The Bactericidal Efficiency of Menthol and Camphor," *American Journal of Pharmacy,* 105:490–500, 1933.

(4) OTC Volume 130136.

p. *Methyl salicylate.* The Panel concludes that methyl salicylate is safe, but that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has evaluated methyl salicylate as a topical anesthetic/analgesic elsewhere in this document. (See part III. paragraph B.3.b. above—Methyl salicylate.)

(1) *Safety.* The safety of methyl salicylate has been described elsewhere in this document. (See part III. paragraph B.3.b.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of methyl salicylate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are no data from controlled studies that establish methyl salicylate as an effective antimicrobial agent. Methyl salicylate is used topically on the skin as a rubefacient and counterirritant. None of the references reviewed by the Panel indicate that the individual ingredient is or has been used as an antimicrobial active ingredient in the mouth and throat (Refs. 1 through 6). A submission to the Panel presented data in support of the antimicrobial activity of methyl salicylate (Ref. 7). These data merely indicate that when methyl salicylate is removed from the tested formulation, which contained other ingredients, bacteriostatic and bactericidal activity was reduced. Data on the antimicrobial activity of the ingredient alone was not presented. The Panel does not consider a study of this type supportive of claims that methyl salicylate is an effective antimicrobial agent.

The Panel concludes that there are insufficient data to establish the effectiveness of methyl salicyclate as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to a 0.4-percent concentration of methyl salicylate in the form of a rinse, mouthwash, gargle, or spray, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 130042.
(2) OTC Volume 130043.
(3) OTC Volume 130044.
(4) OTC Volume 130045.
(5) OTC Volume 130046.
(6) OTC Volume 130047.
(7) OTC Volume 130136.

q. *Oxyquinoline sulfate (8-hydroxyquinoline).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of oxyquinoline sulfate as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Oxyquinoline sulfate is a salt made by reacting oxyquinoline with sulfuric acid.

Oxyquinoline has also been called oxine, 8-hydroxyquinoline, oxybenzopyridine, phenopyridine, 8 quinolinol, and oxychinolin (Ref. 1). The quinolines (n-quinoline and isoquinoline) are derived from naphthalene by substituting a trivalent notrogen atom for a carbon atom in one of the aromatic rings, converting the compound into a tertiary amine. The compound then possesses basic properties and reacts with acids to form salts. A hydroxyl group substituted on position 8 of the aromatic nucleus of quinoline converts it to oxyquinoline and confers phenolic properties. Oxyquinoline, therefore, is both a phenol and an amine and manifiests either acidic or basic properties depending upon the acidity or alkalinity of the solvent in which it is incorporated. Oxyquinoline is manufactured by heating *o*-aminophenol with *o*-nitrophenol, glycerol, and sulfuric acid (H_2SO_4) (Ref. 1).

Oxyquinoline base is a white crystalline powder that is almost insoluble in water and ether, but freely soluble in alcohol, acetone, chloroform, and benzene. It is also soluble in aqueous mineral acids and in glycerol (Ref. 1). Oxyquiniline melts at 76° C and boils at approximately 267° C. Oxzyquinoline is used in industry as a chelating agent to precipitate metals. Oxyquinoline is known in industry as 8-HQ. It is not used in its basic form for medicinal purposes due to its poor water solubility. Oxyquinoline is, however, used in the form of one of its water-solube salts, among which are the sulfate, citrate, tartrate, and benzoate. The most commonly used salt is oxyquinoline sulfate. Oxyquinoline sulfate is a yellow crystalline powder with a slight saffron odor and a burning taste. It melt between 175 and 178° C. It is freely soluble in water; soluble in approximately 1 part in 100 parts of glycerine; slightly soluble in alcohol; and insoluble in ether. The sulfate has been used as a bacteriostatic agent in the treatment of athletes' foot, vaginitis, and as a gargle, eyewash, and in hemorrhoidal preparations (Ref. 2). Oxyquinoline sulfate has been classified as a bactericide, fungicide (especially against candida), and a tichomonacide (Ref. 3).

Oxyquinoline benzoate is a slightly yellow crystalline substance, soluble in water, slightly soluble in alochol, and nearly insoluble in ether and alkaline aqueous sulutions (Ref. 2). It has been used for the same purposes as oxyquinoline sulfate. Oxyquinoline citrate is also a yellow crystalline powder with a saffron-like odor. It is freely soluble in water. Solutions are acid in reaction (Ref. 2).

Various iodinated and chlorinated quinoline derivatives have been or are still in use as amebicides. Among these are iodohydroxyquinoline sulfuric acid, iodochlorohydroxyquinoline, and diiodohydroxyquinoline. They are effective against amebae on the surface of the intestinal mucosa. The parasites in the submucosal tissues are unaffected. They most likely exert their antimicroboal effects by inactivating the enxymes or halogenating the proteins of the amebae.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of oxyquinoline as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Quinoline itself has been suspect for many years. In a study performed in 1881, quinoline (oxyquinoline minus the hydroxyl group) was found to be strongly antiseptic and toxic (Ref.4). It is possible that the presence of hydroxyl group diminishes its toxicity. The administration of 0.2 g/kg subcutaneously and intravenously produced retinitis (Ref. 4). The lesions noted were similar to those produced by naphthalene. Some of the more recently introduced iodo-, chloro-, or iodo- and chloro-substituted quinolines used to threat amebiasis have been found to cause optic nerve atrophy.

The acute toxicity of oxyquinoline sulfate, on the other hand, appears to be low. Gleason (Ref. 5) states that rabbits can tolerate single oral doses of 3.7 g/kg of the sulfate when mixed with posassium sulfate. Rats, guinea pigs, and dogs tolerate large quantities after oral administration. The acute LD_{50} in guinea pigs is 175 g/kg. The LD_{50} in rats is 32 g/kg after 1 week. In dogs there was no mortality. Animal and human data on chronic toxicity are not available. Long-term clinical use of oxyquinoline salts appears to indicate that these derivatives have a low degree of toxicity.

The fate of oxyquinoline in the body was first studied in 1899 and later in 1928 (Ref. 4). It is rapidly absorbed from the intestines of dogs and rapidly excreted into the urine conjugated with sulfuric acid as "ethereal sulfate." Conjugation occurs at the phenolic hydroxyl group. A small part is excreted unmetabolized in the urine and some in the bile. Its metabolic fate in man has not been reported.

Besides the salts of oxyquinoline, monoiodinated derivatives such as iodochlorhydroxyquin and diiodinated derivatives have been used as amebicides.

Skin sensitivity and severe irritation have been reported in workmen during industrial use. Irritation and sensitization have also been reported after repeated application of the salts of oxyquinoline incorporated for topical use on the skin.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of oxyquinoline sulfate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Oxyquinoline sulfate is considered to be primarily bacteriostatic, since it is feebly bactericidal. Its exact mode of action has not been established, but it is believed to act by chelating various metals required by microorganisms for metabolism. Among these are iron, cobalt, copper, and magnesium. Other drugs believed to act in a like manner are salicylates, thiourea, thiouracil, the tetracyclines, cortisone, and penicillin. Oxyquinoline sulfate is presumed to form a copper chelate which easily passes into the cell of an invading pathogen. After the chelate enters the cell it undergoes a chemical change that releases copper which, in turn, kills the organism. Thus, the drug acts by allowing the passage of small amounts of copper chelated from the host's tissues into the invading organism (Ref. 5). It has also been suggested that it may act on the cell membrane and alter its stability and permeability. The amount chelated from the host is not sufficient to cause harm, but is sufficient to adversely effect the microorganisms.

The antimicrobial activity of oxyquinoline in vitro is subject to many influences, such as concentration, temperature, and pH, all of which make its action difficult to predict. It is the consensus of the Panel that if its action in vitro, where variables can be eliminated, is unpredictable, then its in vivo behavioir is less predictable.

Oxyquinoline sulfate has been used in a 1:1,000 solution externally on the skin, in a 1:3,000 aqueous solution as a nasal spray and as an eyewash, in a 1:2,000 aqueous dilution as a gargle, and in a 1:1,000 dilution as a vaginal douche. In dentistry, it is used as an oral antiseptic. A 1- to 2-percent solution is used to treat pus cavities either as an irrigant or soaked in a gauze pack. Oxyquinoline sulfate has also been used internally as an antimicrobial agent for dysentery. Oxyquinoline salts are said to be effective against candida and trichomonas.

Oxyquinoline sulfate manifests no known topical anesthetic properties which relieve pain due to sore throat or sore mouth.

The Panel does not have data from controlled studies on oxyquinoline sulfate's effectiveness as a broad-spectrum antimicrobial agent. Since controlled in vivo studies are not available, the Panel cannot make a judgment concerning the effectiveness of oxyquinoline sulfate as an antimicrobial agent for the treatment of symptoms of sore mouth and sore throat (Ref. 6).

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.1-percent concentration of oxyquinoline sulfate in aqueous solution in the form of a rinse, gargle, or spray not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 644, 1976.

(2) Harvey, S. C., "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1103, 1975.

(3) DerMarderosian, A. H., "Pesticides," *in* "Remington's Pharmaceutical Sciences," 14th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA. p. 1194, 1970.

(4) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., p. 824, 1957.

(5) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 1124–1125, 1970.

(6) "The Merck Index," 5th Ed., Merck and Co., Rahway, NJ, p. 279, 1940.

r. *Phenol.* The Panel concludes that phenol is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has classified phenol as a Category I anesthetic/analgesic and has described its general characteristics elsewhere in this document. (See part III. paragraph B.1.g. above—Phenol.)

(1) *Safety.* The Panel concludes that phenol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has described the safety of phenol elsewhere in this document. (See Part III. paragraph B.1.g.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenol as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenol was the first antimicrobial agent to be used in medicine. Lister first used it in 1967 as a sterilizing agent for surgical instruments and as an antiseptic (Ref. 1). In high concentrations phenol is a protein precipitant; at lower concentrations it is a protein denaturant. Phenol exerts an antimicrobial action by denaturing the protein of living cells. An easily dissociated complex of phenol and the protein is formed. This ability to form a comlex permits the penetration of phenol through the intact or abraded skin, subcutaneous tissues, and mucous membranes with which it comes into contact (Ref. 2).

As is the case with most antimicrobial agents, phenol is not effective against all types of microorganisms. In appropriate strengths (0.5 to 1.5 percent) aqueous solutions of phenol rapidly destroy nearly all forms of bacteria. However, phenol is generally not sporicidal. Anthrax spores may not be killed even after 24 hours exposure to a 5-percent aqueous solution of phenol (Ref. 1). A 1-percent solution destroys nonsporulating organisms after a sufficiently prolonged exposure. A 2-percent solution does so more promptly.

Aqueous solutions of phenol in a proportion of 1:800 are bacteriostatic and inhibit the multiplication of bacteria. Its value as a germicide is due largely to the fact that its activity is only slightly diminished in the presence of proteins. Concentrations of phenol exceeding 1.5 percent also denature the proteins of cells of healthy tissues. For this reason phenol has been supplanted by other antimicrobial agents (Ref. 3).

Phenol has been widely adopted as a standard for comparison of the disinfectant power of antimicrobial agents. According to Harvey (Ref. 2), the concept of using it as a means of comparison of bactericidal power of antimicrobials was originally suggested by Walker and Rideal in 1903. The standard is termed the "phenol coefficient." An antimicrobial agent with a microbial activity equal to that of phenol would have a coefficient of 1.0. An antimicrobial agent killing twice the number of microbes of a particular strain under standard and identical conditions would have a phenol coefficient of 2.0. Some antimicrobial agents when tested against certain organisms have coefficients of over 1,000. For this reason other microbial agents have supplanted phenol as an antiseptic.

The nature of the medium in which phenol is dispersed or dissolved greatly influences its germicidal activity. Generally, aiqueous solutions are the most effective preparations. Phenol has a high oil/water partition coefficient and is slowly released from a lipid phase. Phenol is therefore practically ineffective in fats and animal and vegetable oils when applied topically. In addition, its antibacterial effect is greatly reduced when incorporated in petrolatum. Alcohol and glycerin both diminish its germicidal action while sodium chloride allegedly enhances it. The bactericidal effectiveness of phenol is greatly reduced at low temperatures and in an alkaline medium (Ref. 1).

Phenol is relatively ineffective as an antimicrobial agent when incorporated in soaps. Phenol was once widely used as a disinfectant, for sanitation, and as a germicide for various medical and surgical purposes, but it has been replaced largely by more effective, less toxic compounds. Phenol is fungicidal in concentrations of 1.3 percent or more (Ref. 3).

Even though phenol precipitates and denatures protein, its antibacterial activity continues in the presence of protein because it subsequently

separates from the combination and continues to penetrate into a protein mass, such as sputum, mucus, and other organic materials. Camphor added to phenol in liquid petrolatum greatly reduces the local action and absorption of phenol. Apparently the camphor "holds" the phenol by acting as a solvent or forming a complex. Moisture favors the release of the phenol from the complex. A combination containing 4 percent phenol, 60 percent camphor, and petrolatum is used topically, but the Panel emphasizes that the quantity of phenol released varies with environmental conditions and is not predictable.

Phenol vaporizes slowly, and the vapors may be inhaled. The phenol gains access to the bloodstream via the lungs.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of phenol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.5- to 1.5-percent concentration of phenol in aqueous solution in the form of a rinse, gargle, or spray not more than three to four times daily. Use a lozenge containing 10 to 50 mg of phenol every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 805–809, 1957.

(2) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 987–992, 1975.

(3) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1263–1264, 1975.

s. *Phenolate sodium.* The Panel concludes that phenolate sodium is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenolate sodium as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The Panel has classified phenolate sodium as a Category I anesthetic/analgesic and has described its general characteristics elsewhere in this document. (See part III. paragraph B.1.h. above—Phenolate sodium.)

(1) *Safety.* The Panel concludes that phenolate sodium is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The safety of phenolate sodium has been described elsewhere in this document (See part III. paragraph B.1.h. (1) above—Safety.)

(2) *Effectiviness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenolate sodium as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenolate sodium possesses antiseptic and germicidal properties that are similar to phenol (Ref. 1). These actions are due to the phenol that is released when the compound is dissolved in water. It has been applied to bandages in an aqueous solution or with linseed oil in a ratio of 1 part to 5 to 10 parts of oil for use on the skin. It has been used internally for diarrhea and dysentery, but is not recommended due to its toxic properties. The dose used was 0.1 to 0.3 g. It is no longer used for internal purposes.

The sodium salt is formed with the keto form, one of the two hydrogen atoms on position 2 of the benzine ring being replaced by a metal such as sodium (Ref. 2). Phenolate sodium possesses the same antimicrobial properties as phenol. (See part IV. paragraph B.3.r. above—Phenol.)

Phenolate sodium is used topically in oral health care products when it is necessary to have a phenol-containing preparation that is basic and can act as a buffer and still have the activity of phenol.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of phenolate sodium as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a concentration of phenolate sodium in aqueous solution, equivalent to a 0.5- to 1.5-percent concentration of phenol, in the form of a rinse, gargle, spray, or drops, or by swabbing, not more than three to four times daily. For children under 3 years there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products of oral health care containing antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Stecher, P. G., et al., "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 958, 1960.

(2) Noller, C. R., "Chemistry of Organic Compounds," W. B. Saunders Co., Philadelphia, pp. 489–490, 1951.

t. *Povidone-iodine.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of povidone-iodine (PVP–I) as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There is some disagreement concerning the chemical nature of povidone-iodine. Some believe that it is a specific chemical entity; others claim that it is merely a complex. The prevailing consensus is that povidone-iodine is a complex composed of povidone and elemental iodine. Povidone is a faintly yellow solid which dissolves in water to give a plastic-like colloidal solution. Povidone is also known as 1-ethenyl-2-pyrrolidinone polymers; 1-vinyl-2-pyrrolidinone polymers; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvinylpyrrolidone; polyvidone; and P.V.P. Povidone is made synthetically by interacting 1, 4 butanediol with ammonia and acetylene (Ref. 1).

Povidone was introduced in World War II by the Germans as a substitute for plasma, and as plasma volume expander. A 3.5-percent solution develops osmotic pressure of 400 mm of water. However, it is no longer used for this purpose.

Povidone is available as a series of aggregates having mean molecular weights ranging from 10,000 to 700,000 daltons. Povidone is also soluble in alcohol and chloroform. It is particularly insoluble in ether (Ref. 1). Povidone is used, however, as a solvent for drugs, as a dispersing agent, and to form complexes with various medicinal substances, one of which is iodine. Povidone-iodine is produced commercially by interacting elemental iodine with povidone.

Povidone-iodine consists of yellow flakes which are readily soluble in water. Aqueous solutions have a pH of approximately 2. The addition of sodium bicarbonate makes aqueous solutions less acidic, but also less stable. Freshly prepared solutions of povidone-iodine do not give a blue color with starch as do tinctures and other solutions of elemental iodine. Solutions that have been standing for some time do give a blue color. Aqueous solutions of povidone-iodine are colloidal in nature. Their viscosity varies with the molecular weight of the povidone used to form the complex. When an aqueous solution is applied topically, a slow release of free iodine occurs which exerts an antimicrobial action.

Povidone-iodine is a nonsurfactant type of iodophor and is the only one of this type evaluated by the Panel. Iodophors are complexes of iodine and iodine salts, proteins, and other colloidal organic molecules which release free iodine. They are less irritating to the skin than the tinctures. The iodine that can be released in its free form from povidone-iodine is approximately 10 percent of the total labeled iodine content of the complex.

Elemental iodine is among the most potent antispetics available (Ref. 2). The anticmicrobial effects of iodine are probably due to its iodinating and oxidizing effects on microbial protoplasm. (See part IV. paragraph B.3.n. above—Iodine.) The activity of iodine is reduced by alkaline substances and in the presence of organic matter. This is also true of iodine released from iodophors.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of povidone-iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Povidone is practically nontoxic. Gosselin et al. (Ref 3) rate its toxicity as 1 (practically nontoxic). Povidone has been used as a colloid in salt solutions to increase blood volume in the treatment of hypovolemic shock by intravenous infusion. Povidone is not metabolized. The greatest portion is excreted unchanged by the kidney.

Renal excretion is governed by the size and molecular weight of the particles. Particles whose molecular weights are less than 25,000 daltons are excreted by the kidney. Larger molecules are not filtered by the glomerular membrane or secreted by the tubes of the kidney. Particles of intermediate molecular weight are deposited in the tissues and are slowly excreted over a period of several months to a year. The unexcreted particles are phagocytized by cells in the reticuloendothelial system and stored in the liver, spleen, lung, and bone marrow (thesaurismosis). Such storage has been associated with pathological changes in the lymph nodes. Susceptible individuals who repeatedly inhale substantial quantities, as in hair sprays, and individuals who have used large quantities over long periods of time have been affected and have developed adverse reactions.

Chronic, indiscriminate use of PVP–I has been associated with iodism, an increase in protein-bound iodine, and altered thyroid function. The toxic effects of PVP–I are due to the released free iodine, and since the release occurs slowly its toxicity and irritancy is low. This slow release also raises doubts about its effectiveness, since the active ingredient is elemental iodine.

Recently, Woldkowski, Speck, and Rosenkranz (Ref. 4) have indicated that povidone-iodine is capable of altering DNA in living cells and inducing mutations in salmonella. This is ascribed to the liberated iodine. Because of the known potential and the ability of mutagenic substances to induce cancer in animals, this finding raises serious questions concerning the safety of iodine and iodine-releasing substances used as topical antiseptics on the mucous membranes of the mouth and throat. The halogens, including iodine, are capable of reacting with nucleic acids and their constituents and affecting DNA.

Ferguson, Geddes, and Wray (Ref. 5) recently reported that short-term therapy with a povidone-iodine mouthwash had an adverse effect on 16 healthy individuals after 2 weeks of use. Significant increases occurred in total serum iodide, protein-bound iodine and inorganic iodine, total thyroxine, and free iodine index. The possibility of thyroid suppression following long-term use is also mentioned in this report. The adverse effects of long-term use of potassium iodide are mentioned below. (See Part IX. paragraph B.2. below—Potassium iodide.)

Lagarde, Bolton, and Cohn (Ref. 6) devised experimental models to study the effectiveness of intraperitoneal povidone-iodine in an established peritonitis. In both models there was 100 percent mortality in the povidone-iodine treated group. This study strongly suggests that the intraperitoneal administration of povidone-iodine can be fatal when animals are compromised by peritonitis. The mechanism of this effect is unclear. On the basis of these studies, intraperitoneal administration of povidone-iodine cannot be recommended for therapy of peritonitis.

In another study, Bolton, Bornside, and Cohn (Ref. 7) stated that in dogs with appendicitis-induced peritonitis, intraperitoneal povidone-iodine caused death more rapidly than the instillation of saline solution. The bacterial content of canine peritoneal fluid increased with time, although fewer bacteria were found in fluid from povidone-iodine treated dogs. The differences were not statistically significant. Qualitative chemical analysis of peritoneal fluid revealed iodide but not free iodine. Fifteen to 30 minutes after instillation of povidone-iodine, iodine was present in the peritoneum for 2 hours, but not 3 to 6 hours. The antibacterial effect of povidone-iodine was demonstrated in mice challenged intraperitoneally with lethal doses of *Escherichia coli.* Povidone-iodine diminished mortality, when injected immediately, but not when given 1 to 3 hours later. Immediate injection of povidone-iodine into mice lowered the number of *Escherichia coli* by 3 logs. Injection of povidone-iodine 3 hours after bacterial challenge lowered the number of *Escherichia coli* by only one-third log. This lesser bacterial effect in early treated mice is attributed to greater dispersal and sequestration of bacteria throughout the peritoneal cavity with the inactivation of povidone-iodine by reduction to iodide in vivo. In dogs with appendicitis-induced peritonitis, the more rapid death after treatment with povidone-iodine was not associated with differences in peritoneal microflora, but with peritoneal absorption of excessive amounts of iodide. The ultimate bacterial count in the early treated dogs and those treated with the antiseptic 3 hours after the peritoneal cavity was contaminated

with the same. The mortality likewise was the same.

Although the peritoneum is a serous surface, it does not differ remarkably from a mucous surface. Topical use of povidone-iodine on the peritoneum proved to be of no benefit. It is not unreasonable to assume that this further augments the argument that topical antiseptics on the mucous membranes are of doubtful benefit.

Application of elemental iodine as a tincture to the skin causes direct irritation. On rare occasions iodine gives rise to a hypersensitivity reaction characterized by fever and generalized skin eruptions (Ref. 8). Iodine is rapidly converted to the inactive iodide ion by organic material in the gastrointestinal tract when swallowed.

A study and review of the toxicity of povidone-iodine was performed by Shelanski and Shelanski (Ref. 9), who compared PVP–I to Lugol's solution and tincture of iodine. The three solutions used were formulated to contain equal quantities of free iodine. The oral LD_{50} in rats was 1,300 mg/kg of iodine for the PVP–I complex as compared to 400 mg/kg of iodine for the Lugol's solution. Solutions of PVP–I and tincture of iodine were applied to intact rabbit skin and covered with wax paper. After 24 hours, severe erthema developed, and the paper over the area to which the iodine tincture was applied had to be removed. No reaction was noted 96 hours after application of the PVP–I. The same response was obtained after reapplication 2 weeks later. When the same sequence was carried out on 200 human subjects, similar results were obtained, i.e., a severe reaction to the iodine occurred within 24 hours, and no reaction to PVP–I was observed after 96 hours. Reapplication 2 weeks later also showed no reaction to PVP–I after 48 hours. The PVP–I and Lugol's solution were also tested by daily instillation into the eyes of rabbits and guinea pigs for 2 weeks. PVP–I produced slight reddening which disappeared after 3 days while the eyes instilled with Lugol's solution showed severe erythema, edema, and progressive corneal damage. The investigators concluded from these observations that PVP–I is less toxic, less irritating, and less sensitizing than Lugol's solution or tincture of iodine.

Extensive clinical observations also indicate that PVP–I is generally nonirritating and nonsensitizing when applied to the skin and mucous membranes. For example, Connell and Rousselot (Ref. 10) studies the antiseptic effect of PVP–I applied to the skin of 345 patients either preoperatively, for the treatment of skin infections, or for burns. Additionally, surgeons and ward personnel used PVP–I as a surgical hand scrib. At no time did any patient or physician develop any sensitivity to the PVP–I. Three volunteers used the test preparation one to five times daily for over 2 years with no signs of any injurious reaction. The investigatiors, therefore, concluded that PVP–I was not only highly effective as an antiseptic agent, but also noninjurious to both normal skin and open wounds.

Although two cases of desquamation due to PVP–I used as a preoperative topical antiseptic have been reported by another investigator (Ref. 11), unusual and similar circumstances were noted in each case, i.e., long exposure combined with an elevated body temperature (100° F) resulting from the use of a heating blanket. When these conditions were avoided no further difficulty was encountered.

The marketing experience of industrial products also suggests that PVP–I is relatively nontoxic and nonirritating for use on the skin and mucous membranes. PVP–I has also been widely used by consumers over the past 6 to 7 years with no reports of untoward results (Ref. 12).

The fact that a single application of PVP–I is innocuous on the oral mucosa over a limited area is apparent from reports in the dental literature. However, safety following chronic, long-term use in the entire oral cavity has not been established. Well-controlled studies on the effects of repeated applications on the mucous membranes of the mouth and throat, as would be used in a daily gargle or oral rinse are not available. Six studies are cited in which PVP–I was used as a gargle by a total of over 3,000 patients without untoward effects. In two of these studies, the drug was used more than once (Refs. 12 and 13). In a study that was controlled, no irritation occurred after 2 to 3 applications in 25 patients. The other five studies were uncontrolled. There were insufficient details concerning the experimental design for an evaluation of safety to be made (Ref. 9).

In the opinion of the Panel, PVP–I may be safe for occasional application to the mucous membranes, but there are insufficient data to establish its safe use on a long-term, daily basis as a rinse, mouthwash, or spray on the mucous membranes of the mouth and throat. There is some evidence that long-term use may result in adverse effects from both the povidone and the free iodine that is released (Refs. 12 and 13).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of povidone/iodine as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Povidine-iodine, as is the case with elemental iodine, is effective against both gram-negative and gram-positive organisms. The antimicrobial effect of povidone-iodine is due to release of elemental iodine from the complex. PVP–I is, however, generally less effective than the tincture and other iodine solutions (Ref. 14).

The effectivensss of iodophors against both gram-negative and gram-positive organisms is an advantage over hexachlorophene. The iodophors do not persist in the skin to provide cumulative, continuing antibacterial activity as does hexachlorophene (Ref. 15). The dental and medical literature contains a number of studies suggesting that PVP–I is rapidly germicidal for many oral cavity microorganisms. Its application on the injection site of the oral mucosa prior to administering local anesthesia virtually eliminates all readily cultivable organisms (Refs. 16, 17, and 18). However, it must be remembered that this rapid germicidal action is achieved at an oral site having a relatively small microbial population. The possibility of a carry-over of PVP–I into the culture medium also was not considered in any of the studies reviewed by the Panel.

Three studies indicate that irrigation of the gingival sulcus and rinsing the mouth with PVP–I immediately before tooth extraction or gingivectomy markedly reduces the incidence of associated bacteremia (Refs. 19, 20, and 21). Unfortunately the results of two of these studies have been published only in abstract form, and the data presented are insufficient in detail to be properly evaluated. The third was a study in which 32 patients were treated similarly, one with the povidone-iodine and the other group with an aqueous placebo solution (Ref. 21). Bacteremia occurred in 28 percent of the PVP–I treated group as compared to 56 percent of the placebo group (P is less than 0.01 by chi-square analysis). Cultures taken from gingival sulcus before and after the preoperative treatment indicated that there was some decrease in numbers of microorganisms among the PVP-I-treated group, but since quantitative culture methods were not used, the Panel does not consider these data to be meaningful.

Despite extensive studies on PVP–I applied to the skin, its antiseptic effectiveness in controlling the microbial population was still doubted by the Advisory Review Panel on OTC

Antimicrobial Drug Products for reasons which are also of concern when evaluating it as an oral antiseptic (39 FR 33130–33131). These concerns are as follows:

(i) The rate of "slow-release" of free iodine from PVP–I is variable and not known, particularly in the presence of ill-defined organic material, which may be present on the skin in varying quantities under variable circumstances.

(ii) The germicidal activity of the preparation during the "slow-release" period has not been defined and is not known.

(iii) There is conflicting evidence as to whether PVP–I accelerates or delays wound healing.

(iv) The stability of the preparation during various conditions of storage ge a25my2.254has not yet been determined.

(v) The rate of absorption of the free iodine from the mucous membranes is now known.

(vi) The rate of absorption of the povidone complex with the iodine from the mouth and throat is now known and its potential for producing enlarged lymph nodes has not been determined. The iodine is suspect as a carcinogen, and this, combined with the effect povidone may already have in this regard, are now known.

One study utilizing 262 patients is cited in a product submission (Ref. 12). All but four patients noted symptomatic relief from throat irritation, soreness, dryness, and hoarseness. These evaluations again were subjective and do not provide the Panel with adequate data to make an evaluation.

Povidone-iodine manifests no known topical anesthetic properties which relieve pain due to sore throat and sore mouth.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of povidone-iodine as an antimicrobial agent of the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 7.5-percent concentration of povidone-iodine diluted 1:14 or a 0.5-percent concentration of povidone iodine in the form of a rinse, mouthwash, gargle, spray, or as a swab, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Rahway, NJ, pp. 996–997, 1976.

(2) Abramowicz, M., "Topical Antiseptics and Antibiotics," *The Medical Letter on Drugs and Therapeutics,* 19:83, 1977.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 245, and section III, pp, 181–182, 1976.

(4) Wlodkowski, T. J., W. T. Speck, and H. S. Rosenkranz, "Genetic Effects of Povidone-Iodine," *Journal of Pharmaceutical Sciences,* 64:1235–1237, 1975.

(5) Ferguson, M. M., D. A. M. Geddes, and D. Wray, "The Effect of a Povidone-Iodine Mouthwash Upon Thyroid Function and Plaque Accumulation," *British Dental Journal,* 144:14–16, 1978.

(6) Lagarde, M. C., J. S. Bolton, and I. Cohn, "Intraperitoneal Povidone-Iodine in Experimental Peritonitis," *Annals of Surgery,* 187:613–619, 1978.

(7) Bolton, J. S., G. H. Bornside, and I. Cohn, Jr., "Intraperitoneal Povidone-Iodine in Experimental Canine and Murine Peritonitis," *American Journal of Surgery,* 137:780–785, 1979.

(8) Seymour, W. B., "Poisoning from Cutaneous Application of Iodine: A Rare Aspect of its Toxicologic Properties," *Archives of Internal Medicine,* 59:952–966, 1937.

(9) Shelanski, H. A., and M. V. Shelanski, "PVP-Iodine: History, Toxicity and Therapeutic Uses," *Journal of the International College of Surgeons,* 25:727–734, 1956.

(10) Connell, J. F., and L. M. Rousselot, "Povidone-Iodine: Extensive Surgical Evaluation of a New Antiseptic Agent," *American Journal of Surgery,* 108:849–855, 1964.

(11) Llorens, A. S., "Reaction to Povidone-Iodine Surgical Scrub Associated with Radical Pelvic Operations," *American Journal of Obstetrics and Gynecology,* 114:834–835, 1972.

(12) OTC Volume 130056.

(13) OTC Volume 130057.

(14) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 887, 1977.

(15) Abramowicz, M., "Chlorhexidine and Other Antiseptics," *The Medical Letter on Drugs and Therapeutics,* 18:86, 1976.

(16) Jablon, J. M., D. D. Zinner, and M. S. Saslaw, "The Use of Polyvinylpyrrolidone Iodine as an Oral Antiseptic," (abstract), *Dental Abstracts,* 3:615, 1958.

(17) Zinner, D. D., J. M. Jablon, and M. S. Saslow, "Bactericidal Properties of Povidone-Iodine and Its Effectiveness as an Oral Antiseptic," *Oral Surgery Oral Medicine and Oral Pathology,* 14:1377–1382, 1961.

(18) Blake, G. C., and G. H. Forman, "Pre-operative Antiseptic Preparation of the Oral Mucous Membrane: A Bacteriological Assessment," *British Dental Journal,* 123:295–298, 1967.

(19) Brenman, H. S., and E. Randall, "Reduction of Gingival Bacteria and Gingivectomy-Related Bacteremia by Povidone-Iodine," *International Association of Dental Research,* (Abstract #211), 1972.

(20) Randall, E., and H. S. Brenman, "Antimicrobial Action of Povidone-Iodine Mouthwash Before and During Dental Prophylaxis," *Journal of Dental Research,* 51:101, 1972.

(21) Scopp, I. W., and L. D. Orvieto, "Gingival Degerming by Povidone-Iodine Irrigation: Bacteremia Reduction in Extraction Procedures," *Journal of the American Dental Association,* 83:1294–1296, 1971.

u. *Secondary amyltricresols.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of secondary amyltricresols as OTC antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Amyltricresols are prepared by the interaction of ortho-, meta-, and para-cresols and secondary amyl alcohol at 150° C. This results in a mixture of isomeric secondary amyltricresols. The amyl radical substitutes into the ring. The substitution of alkyl groups into the aromatic ring of a phenolic compound increases the bactericidal effects of the phenol (Ref. 1). The three isomeric cresols have a phenol coefficient of 3, while secondary amyltricresols have a phenol coefficient of 100 or more, depending upon the organism tested. In one study using the FDA method, the mixture had a phenol coefficient of 14 for *Salmonella typhosus* and 100 against streptococci (Ref. 2). These amyltricresols lower surface tension, which allows them to become evenly distributed over cell membrane surfaces (Ref. 3).

The secondary amyltricresols are relatively insoluble in water, but are soluble in alcohol. They are usually dissolved in 30-percent alcohol for use as disinfectants. The presence of environmental proteins, such as blood, serum, mucus, and cellular debris, decreases the bactericidal activity of secondary amyltricresols, but their presence eliminates the bacteriostatic activity completely. Solutions of 1:30,000 inhibit the growth of molds and bacteria. The amyltricresols have been used since 1931.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of secondary amyltricresols as OTC antimicrobial active ingredients for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limits set forth below.

Oral administration of amyl metacresol in rats revealed a slight reddening of the mucosa of the intestines and stomach in doses of less than 1 g/kg. The minimal lethal oral dose in the rat is 2.5 to 4.5 mg/kg (Ref. 4). In a chronic oral toxicity study, rabbits were fed 0.6 g of anyl metacresol without manifestations of toxic symptoms (Ref. 4). The urine and feces were examined daily and no blood, albumin, pus cells, or casts were found. In a study in humans, six subjects were given the drug orally. No toxicity was noted (Ref. 5).

The only human clinical data submitted were from a study in which oral wounds were treated with a commercial preparation containing secondary amyltricresols (Ref. 5). The commercial preparation was compared with standard disinfectants. The amyltricresol preparation was shown to cause no apparent signs of toxicity to the tissues.

No data were available to the Panel concerning the rates of absorption from the mucous membranes of the mouth and throat, irritancy, potential for sensitization, or metabolic fate and elimination of these cresols. Data on tumorigenic, mutagenic, and teratogenic effects of secondary amyltricresols, when used over long periods of time, are not available. There is a paucity of data on chronic toxicity from prolonged use. Little data are available on the long-term use of the lesser known and less frequent use of such phenols. The Panel therefore recommends that they be used only for short-term use.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of secondary amyltricresols as OTC antimicrobial agents for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The secondary amyltricresols are bactericidal in a 1:4 dilution and will kill the following bacteria:

Bacterium	Time (seconds)
Salmonella typhosa	50.
Streptococcus pyogenes	20.
Staphylococcus aureus	20 to 30.
Diphtheriae pneumonia	5.
Alpha-hemolytic streptococcus	5.
Diphtheroids	20 to 40.

The same dilution kills *Escherichia coli* and *Pseudomonas aeruginosa* after a 4-minute exposure. *Streptococcus viridans* (alpha-hemolytic streptococci) is killed in 5 seconds and other gram-positive organisms in 5 seconds when exposed to dilutions used in the commercial preparation. Secondary amyltricresols are not sporicidal (Refs. 5 and 6).

The seconday amyltricresols are bacteriostatic. The growth of *Staphylococcus aureus* was inhibited in the presence of plasma after exposure for 5 minutes. The growth of *Streptococcus viridans* was inhibited after exposure for 10 minutes, and the growth of *Salmonella typhosa* was inhibited after exposure for 5 minutes. The growth of a gram-positive sporulating organism was inhibited after 21 hours at a concentration of 1:150 to 1:160 (Ref. 4).

The secondary amyltricresols will kill most gram-positive bacteria and some gram-negative bacteria. No data were submitted demonstrating their effectiveness and bactericidal or bacteriostatic activity against the flora of the oral cavity.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of secondary amyltricresols as antimicrobial agents for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.1- to 0.3-concentration of secondary amyltricresols in aqueous solution in the form of a rinse, mouthwash, or gargle, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Harborne, J. B., "Biochemistry of Phenolic Compounds," Academic Press, New York, p. 483, 1964.

(2) Coulthard, C. E., J. Marshall, and F. L. Pyman, "The Variation of Phenol Coefficients in Homologous Series of Phenols," *Journal of the Chemical Society,* 133:280–291, 1930.

(3) Burger, A., "Medicinal Chemistry," 3d Ed., Wiley-Interscience, New York, p. 633, 1970.

(4) Broom, W. A., "A Note on the Toxicity of Amyl-Meta-Cresol," *British Journal of Experimental Pathology,* 2:327–331, 1931.

(5) OTC Volume 130013.

(6) McClesky, C. S., and E. Swingle, "A Comparative Study of the Germicidal Activity of Certain Compounds," *Iowa State College Journal of Science,* 11:177–183, 1937.

v. *Sodium caprylate.* The Panel concludes that sodium caprylate is safe, but that there are insufficient data available to permit final classification of the effectiveness of sodium caprylate as an OTC antimicrobial active ingredient for topical use in the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Sodium caprylate is the sodium salt of caprylic acid (octanoic acid) ($Ch_3(CH_2)_6COONa$), an aliphatic, straight-chained carboxylic acid. It is the salt of a lower molecular weight fatty acid and may be considered to be a soap of an eight-carbon, fully saturated acid. Sodium caprylate may be prepared by neutralizing caprylic acid with sodium carbonate or sodium hydroxide. It is freely soluble in water and sparingly soluble in alcohol (Ref. 1). It is poorly ionized to the sodium and caprylate ions in water. Sodium caprylate is one of several fatty acids, such as undecylenic and propionic, that have been used as fungistatic agents topically.

Sodium caprylate has been used as a fungicide and fungistatic agent for the treatment of thrush, tinea pedis (athlete's foot), tinea cruris (jock itch), and other superficial fungous infections of the skin and mucous membranes, particularly those due to trichophyton, microsporon, and candida (Ref. 1). Both the acid and salt were used in the treatment of candidiasis before antibiotics became available. The salt has had limited usage in dentistry as a component of an endodontic medication advocated by Grossman and Christian (Ref. 2), Fajarda, Grossman, and McShane (Ref. 3), and Sawinksi and Gurney (Ref. 4). They reported that it inhibited the growth of *Candida*

albicans in concentrations of 0.03 to 5.0 percent.

Sodium caprylate has also been shown to be effective in the treatment of athlete's foot, when applied in the form of a 10-percent ointment (Ref. 5). It has been used as a dusting powder in a strength of 10 percent, in an inert powder, either along or with other octanoates. Aqueous solutions of 5, 10, and 20 percent sodium caprylate have been administered topically to the skin or mucous membranes. A 5-percent solution has been used as a douche and 10 to 20 percent solutions have been used in the oral cavity.

(1) *Safety.* The Panel concludes that sodium caprylate is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

There are few data on animal or human toxicity of sodium caprylate. However, since the fatty acids appear in many foods and are consumed as such, it is the consensus of the Panel that sodium caprylate, likewise, is safe.

Cohen (Ref. 6) reported using sodium caprylate in a concentration of 50 mg/mL orally and intravenously to treat albino rabbits infected with *Coccidioides immitis.* After sacrificing the animals, postmortem examinations revealed no pathologic effects in any organ in any of the animals. In the same study, 3-g doses of 5 percent sodium caprylate in 5 percent glucose were administered to human subjects intravenously every day for 3 months. The maximum dosage given was 8 g per day. As was the case in the aminal study, no adverse drug reactions occurred.

Cohen and Persky (Ref. 7) have reported treating a series of 12 cases of thrush with a 10-percent aqueous solution of sodium caprylate. The infections responded favorably to the treatment. There were no adverse reactions noted to the drug nor were there any recurrences among the 12 individuals treated. They also reported using 10 percent aqueous sodium caprylate as a routine hospital treatment in both nurseries as well as in the outpatient department.

It is the belief of the Panel that when taken internally, sodium caprylate would probably be metabolized in the same manner as other fatty acids, and that catabolic fatty acid pathways are utilized. No unique toxicity would be expected.

In marketing experience dating back to 1963, 20 nonspecified adverse reactions have been reported (Ref. 9).

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of sodium caprylate as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Like other soaps, sodium caprylate acts as a surfactant, detergent, and emulsifier. This action is due to the caprylate ion, which is an anion. Keeney (Ref. 8) overcame infection of thrush due to *Candida albicans* by local swabbing of lesions of the entire mouth three times daily with a 20-percent aqueous solution of sodium caprylate. Thrush is a mycotic disease of the mouth, throat, and upper digestive tract. (See part II. paragraph B.4.b.(8) above—Candidiasis.) It is characterized by the formation of white plaques within the oral cavity, often coalescing to form a false membrane on the mucosa. It occurs more commonly in debilitated persons.

Cohen and Persky (Ref. 7) confirmed Keeney's findings. They reported dramatic results in 12 cases using a 10-percent aqueous sodium caprylate solution rubbed on the buccal and lingual tissues four times daily. Four days was the average time required to rid the mouth of the fungus. The 10-percent solution benefited all 12 cases of thrush and appeared to cure the infection with no complications or recurrences.

Cohen (Ref. 6) studied the effects of sodium caprylate and three other fungicides on *Coccidioides immitis* using in vitro studies. The fungicidal concentration of sodium caprylate ranged between 19 and 150 mg/mL. In addition, in vivo studies on albino rabbits were performed using 50 mg/mL orally and intravenously per 2.5-kg animal. Cohen concluded that sodium caprylate is effective on the mucous membranes of the mouth and throat and also in sinuses harboring coccidioidal spherules.

A sodium caprylate ointment was shown to have fungistatic activity and possess antibacterial action against *Staphylococcus aureus* and beta-hemolytic streptococcus, though in this respect the ointment is inferior to one prepared from propionic acid and propionate (Ref. 9).

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of sodium caprylate as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 10.0- to 20.0-percent concentration of sodium caprylate in the form of a spray or by swabbing onto lesions in the mouth and throat, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Date Required for Evaluation.)

References

(1) Council of the Pharmaceutical Society of Great Britain, "British Pharmaceutical Codex," The Pharmaceutical Press, London, pp. 698–699, 1954.

(2) Grossman, L. I., and C. K. Christian, "End-Point Study of Bactericidal Effect of Antibiotics Used in Endodontics," *Journal of Dental Research,* 31:42–46, 1952.

(3) Fajarda, O. P., L. I. Grossman, and J. McShane, "An In Vitro Study of Antiseptics and Antibiotics Used in Endodontics," *Journal of Dental Research,* 35:656–659, 1956.

(4) Sawinski, V. J., and B. F. Gurney, "Antifungal Evaluation of a New Endodontic Antiseptic," (abstract), *Journal of Dental Research,* 43:749, 1964.

(5) Keeney, E. L., et al., "Sodium Caprylate: A New and Effective Treatment for Dermatomycosis of the Feet," *Bulletin of Johns Hopkins Hospital,* 77:422–436, 1945.

(6) Cohen, R., "Four New Fungicides for Coccidioides immitis: 1. Sodium Caprylate. 2. Ethyl Vanillate. 3. Fradicin. 4. Thiolutin," *Archives of Pediatrics,* 68:259–264, 1951.

(7) Cohen, R., and M. Persky, "Sodium Caprylate Treatment for Thrush," *Archives of Pediatrics,* 68:33–34, 1951.

(8) Kenney, E. L., "Sodium Caprylate: A New and Effective Treatment for Moniliasis of the Skin and Mucous Membranes," *Bulletin of the Johns Hopkins Hospital,* 78:333–339, 1946.

(9) Osol, A., et al., "The Dispensatory of the United States of America," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 1588, 1947.

w. *Thymol.* The Panel concludes that thymol is safe, but that there are insufficient data to permit final classification of the effectiveness of thymol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol, also known as thyme camphor, is methyl isopropyl phenol. It is therefore an aromatic alcohol. Thymol

possesses topical anesthetic/analgesic properties and has been described elsewhere in this document. (See part III. paragraph B.3.c. above—Thymol.)

(1) *Safety.* The Panel concludes that thymol is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The safety of thymol has been described elsewhere in this document. (See part III. paragraph B.3.c.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The assumption has been made the because thymol is a constituent of one of the various "volatile oils" used in the mouth and throat, it is an effective antimicrobial agent. Its activity is presumably due to its lipophilic properties, which favor penetration into the cell membrane. A 1- to 5-percent solution of thymol in alcohol is used on the mucous membranes to treat herpes. Sollmann (Ref. 1) states "its actions are similar to those of phenol." Thymol's bacteriostatic efficiency is higher than that of phenol in restraining the growth of "pus organisms" in a 1:3,000 dilution. Sollmann also states that "it is not a very effective germicide" and that "thymol has a pleasant clean taste." The text also states that "a saturated watery solution makes a rather agreeable and fairly efficient antiseptic and deodorant mouthwash or gargle, and lotion for discharging wounds."

Thymol has a high phenol coefficient (25), but its antimicrobial activity is greatly impaired by the presence of organic matter (Ref. 1). For instance, the addition of dried feces to an antimicrobially active solution reduces the activity of thymol by two-thirds. It reduces that of phenol by one-third. Thymol is active against yeasts, molds, and fungi. It has been used to treat fungal skin infections with fair success.

Esplin (Ref. 2) writes that, "Thymol and its derivatives, principally chlorothymol, possess both bactericidal and fungicidal properties." Thymol is chiefly of value as a fungicide. It was formerly employed as an anthelmintic, administered orally against certain worms.

The "United States Dispensatory" (Ref. 3) states that "thymol was introduced as a disinfectant with uses similar to those of phenol but with the advantage of having a more agreeable odor. In the absence of organic matter, it is more potent than phenol, but in the presence of large amounts of proteins its activity is greatly reduced." Because of this reduction in activity and because it is a strong irritant, thymol is of little value for use on open wounds or on the mucous membranes of the mouth and throat. Thymol is fungicidal and may be used in the treatment of a variety of fungous infections of the skin. Thymol was formerly used for its antiseptic action in the stomach and intestines. It stimulates peristalsis and may cause diarrhea. Thymol is absorbed from the intestine when ingested orally. About 50 percent of it is conjugated with glycuronic and sulphuric acids, and the conjugate is excreted into the urine.

In a submission to the Panel, a mixture of thymol, menthol, eucalyptol, and methyl salicylate was tested for antimicrobial activity (Ref. 4). It was allegedly found that thymol possessed antimicrobial activity. The testing was not performed using the individual ingredient but by removing the thymol from the mixture and determining the effectiveness of the mixture when the thymol was not present. The mixture, minus thymol, had less antimicrobial activity than when thymol was present. The Panel does not consider these data to be proof of the effectiveness of thymol as an antimicrobial agent when used as a single ingredient.

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of thymol as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 0.006- to 0.1-percent concentration of thymol in the form of a rinse, mouthwash, gargle, or spray not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227–228, 1957.

(2) Esplin, D. W., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 1037, 1970.

(3) Osol, A., et al., "The Dispensatory of the United States of America," 1950 Ed., J. B. Lippincott Co., Philadelphia, pp. 1218–1219, 1950.

(4) OTC Volume 130136.

x. *Thymol iodide.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of thymol iodide as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol iodide is also known as dithymol diiodide (Ref. 1). Thymol iodide was originally considered to be official and was listed in the "United States Pharmacopeia." It is a red-yellow or red-brown powder. It is made by treating a solution of thymol with potassium iodide and sodium hydroxide. Two molecules of thymol interact with one molecule of iodine, and the hydrogen atom on the hydroxyl group of each thymol molecule is substituted with an iodine atom. Thymol iodide has a slightly aromatic odor. It is insoluble in water, glycerin, carbon disulfide, and liquid paraffin; it is soluble in chloroform, ether, collodion, and oils, and slightly soluble in alcohol. Thymol iodide must be protected from light. If exposed to light it undergoes decomposition to free iodine and iodinated derivatives of thymol. Thymol iodide is incompatible with ammonia, mercury bichloride, hydroxides of potassium and sodium, and their carbonates. It gives off vapors of iodine when heated above 100° C.

(1) *Safety.* The Panel concludes that there are insufficient data available to permit final classification of the safety of thymol iodide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

When thymol iodide is applied to tissues, it slowly releases thymol and iodine. This is the basis of its alleged antimicrobial action. It behaves like an iodoform in this respect. Data on the

LD_{50} in animals and on human toxicity were not available to the Panel. The Panel assumes that the toxic effects, if ingested orally, would be due to, and be similar to, those of free iodine. Thymol iodide contains 53 percent iodine by weight. When used externally in dusting powders, it is considered to be nontoxic. Data on systemic toxicity, particularly after long-term use, were not available to the Panel (Ref. 2). Recent evidence indicates that long-term use of iodine-releasing compounds may be mutagenic and alter thyroid function by causing increased activity at first and suppressed activity later. The Panel cautions that this may also occur with long-term use of thymol iodide.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of thymol iodide as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Thymol iodide is similar to iodoform in its properties and behavior. The compound is a water-insoluble, reddish-brown bulky powder containing 43 percent iodine. It is used as an antiseptic dusting powder. It was sometimes employed in an ether solution in which form it has been successfully used as a 25-percent concentration in ether for the treatment of chancroid ulcers. Thymol iodide is effective against *Staphylococcus aureus.*

Thymol iodide is one of the few drugs which are effective in the treatment of actinomycosis. It has been used for this purpose to treat skin lesions. Thymol iodide has also been used in ointments in concentrations ranging from 2 to 10 percent. It has been used externally as an antimicrobial agent and internally as a source of iodine.

The Panel concludes that there is insufficient evidence from controlled studies to establish the effectiveness of thymol iodide as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use a 2- to 10-percent oil solution of thymol iodide by swabbing or applying digitally to the affected area, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling).

(5) *Evaluation.* Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1214, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 7th Ed., W. B. Saunders Co., Philadelphia, PA, p. 817, 1948.

y. *Tolu balsam.* The Panel concludes that tolu balsam is safe, but that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC antimicrobial active ingredient for topical use on the mucous membranes of the mouth and throat.

(1) *Safety.* The Panel concludes that tolu balsam is safe as an OTC antimicrobial agent for topical use on the mucous membranes of the mouth and throat.

The characteristics and data on the safety of tolu balsam are described elsewhere in this document. (See part IX. paragraph B.3.c(1) below—Safety.)

One manufacturer (Ref. 1) submitted the premise that "tolu balsam is well known abroad in preparations for the treatment of sore throat." However, no supporting data were given.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC antimicrobial ingredient for topical use on the mucous membranes of the mouth and throat.

Tolu balsam is a naturally occurring mixture of resins, volatile oils, and organic acids. It contains 12 to 15 percent free cinnamic and benzoic acids and approximately 40 percent benzyl esters of these acids (Ref. 2). It contains a concentration of 1.5 to 3 percent volatile oils. The effectiveness of these acids, esters, and volatile oils as antimicrobial agents is unknown. Benzoic acid has been evaluated by the panel and placed in Category III as an antimicrobial activity. The Panel has likewise considered the antimicrobial activity of volatile oils. In view of the fact that their composition is so variable, the Panel concludes that it is impossible to classify them as effective antimicrobial agents. (See part IV. paragraph A.9. above—Volatile oils.)

Tolu balsam has a feeble stimulating expectorant activity and formerly was used widely in the formulation of various cough syrups (Ref. 2). It is usually employed in the form of tolu balsam syrup which was once official and was included in the "United States Pharmacopeia" and "National Formulary." The balsam is an ingredient found in the compound benzoin tincture. Inhalation of the vapor generated by heating the balsam was also used for the treatment of respiratory infections. Tolu balsam has been employed occasionally in the treatment of contaminated wounds for its "stimulating and antiseptic" activity. No data are supplied indicating the spectrum and the degree of antimicrobial activity. It has also been used for scabies (Ref. 3)

The Panel concludes that there are insufficient data from controlled studies to establish the effectiveness of tolu balsam as an antimicrobial agent for the treatment of symptoms such as sore mouth and sore throat.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage for tolu balsam.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care antimicrobial active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care antimicrobial agents. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 130052.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 126, 1976.

(3) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 1236, 1975.

(4) Osol, A., et. al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1440–1441, 1955.

Category III Labeling

Proposed indication. "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth."

C. Data Required for Evaluation

The Panel agrees that the protocols recommended in this document are in keeping with the sciences of pharmacology and theraupeutics and the art of medicine and do not preclude improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of experimental protocols for testing antimicrobial agents.* The Panel has reviewed the data submitted for antimicrobial active ingredients in OTC oral health care products for topical use on the mucous membranes of the mouth and throat. The Panel has made the suggestions outlined below concerning requirements for protocols for conducting studies to obtain data for reclassifying Category III antimicrobial active ingredients to Category I for safety or effectiveness or both.

The Panel has identified and evaluated two categories of products containing antimicrobial active ingredients; those used on a short-term basis to relieve symptoms of sore mouth or sore throat or both due to microbial infections and those used on a long-term, often on a day-to-day, basis, for cleansing the mouth, suppressing mouth odors, and other related purposes in which no symptoms of an infectious process are evident but for which use antimicrobial claims are made. The ingredients in formulations evaluated in both categories of products include rinses, gargles, sprays, drops, and other solutions for local application, ointments, lozenges, troches, and powders. The method of application and usage may introduce variable factors that must be given consideration in preparing protocols for evaluation of an ingredient. The Panel recognizes that antimicrobial-containing oral health care products are intended to be used to treat and relieve symptoms due to inflammatory processes and that these pathologic states have diverse etiologies. Therefore, it is impossible to propose a single general protocol that would yield data to substantiate claims for safety and effectiveness made for all antimicrobial ingredients submitted for consideration. Obviously, appropriate individual tests must be devised or chosen that adequately establish the safety and effectiveness of an ingredient for a claimed indication or several claimed indications on the labeling.

The Panel expects that the data obtained from the chosen tests show that preparations applied to the mucous membranes of the mouth and throat act topically and reduce pathogenic microbial populations to levels that are therapeutic and that relieve symptoms caused by the infection. The Panel is aware of the fact that differences in usage may introduce uncontrollable, variable factors that make testing difficult.

In its evaluation of the clinical effectiveness of these antimicrobial ingredients, the Panel was aware of the fact that they enjoy widespread OTC use for treatment of pathologic states of the mouth and throat due to amtimicrobial activity. The Panel also recognizes that the consumer has the right to self-diagnosis and self-treatment. The Panel concedes that the average consumer may, in most cases, recognize the signs for symptoms of occasional minor infections in the mouth and throat and should therefore have the option of using an OTC medication for short-term treatment. The Panel believes this should be the case provided the consumer is fully protected by warnings in the labeling, should the symptoms be due to a serious illness not amenable to use of OTC antimicrobial agents, and that the manufacturer has clearly and convincingly demonstrated justification for the claims for such use. The Panel is willing to recommend acceptance of realistic therapeutic labeling claims for effectiveness in treatment of minor, occasional, self-limited infections for short-term use.

The Panel expects the data submitted to demonstrate that the relief of symptoms is due to the antimicrobial effects of an ingredient and that the symptoms recede and may even ultimately disappear after the recommended periods of application.

Demonstration of clinical effectiveness must include proof that the formulated topical antimicrobial product is more effective than the vehicle in which the ingredient is incorporated. The Panel recommends controlled studies that demonstrate that each active ingredient in a combination product for which an antimicrobial claim is made does indeed manifest the antimicrobial activity that is claimed and is not merely an inert vehicle or substance inducing a beneficial placebo effect in the mouth and throat. The Panel requires that evidence be submitted to verify that each antimicrobial agent is successfully released from its vehicle when applied to mucous membranes and thereby becomes available to act on microorganisms within the mucosal layers to which they are applied or with which they come into contact.

2. *Methods of study.* The Panel recognizes that three areas of effectiveness of an ingredient may have to be evaluated: (a) Effectiveness in the treatment of infections by an antimicrobial action. This is a mandatory requirement for study since these claims are made for all antimicrobial agents reviewed. (b) The effectiveness on wound management. By "wound management" the Panel is referring adverse effects on healing or beneficial effects on healing. It must be shown that delays in healing of ulcerations and sloughs of the mucosa caused by the ingredient do not occur. Claims that an ingredient promotes or accelerates wound healing must be substantiated by appropriate, convincing tests and data. (c) Effectiveness for propfhylaxis. It a prophylactic claim is made for an ingredient, the symptoms or pathologic process that are prevented from developing and the types of microorganisms that are killed or prevented from proliferating must be identified. It must be shown that the claimed prophylaxis does indeed occur.

The Panel recognizes that difficulties may be encountered in obtaining acceptable in vivo data concerning specific antimicrobial activity which can be used to establish effectiveness. Therefore, the Panel suggests that preliminary well-designed and well-controlled in vitro studies be performed, the data of which can be verified and supported by in vivo animal and human model studies. Human model studies should be followed by appropriate clinical trials. Such investigational models should simulate as closely as possible situations that would be encountered in actual clinical practice.

The recommendations outlined above and below for testing of effectiveness are not intended to be mandatory requirements. They are presented merely to indicate the types of data considered necessary and to provide suggestions for obtaining such data. It is the consensus of the Panel that the responsibility of selecting or devising reliable methods for procuring acceptable evidence of effectiveness of an ingredient rests with the individuals sponsoring or promoting the product and not with FDA.

a. *In vitro testing.* In vitro testing should include the following: A technique that insures that a carryover of the antimicrobial ingredient into the test system is eliminated by proper dilution or inactivation of the ingredient;

Determination of the spectrum of antimicrobial activity of the agent using both standard cultures and recently isolated strains of each microbial species;

Determination of the minimal inhibitory concentration (MIC) of the antimicrobial agent under standard conditions and against standard reference organisms; and

Testing freshly obtained clinical isolates from mouth or throat infections to provide updated, relevant data on susceptibility of these isolates to an antimicrobial agent.

The Panel has described below an in vitro test that may be found useful as a guide in formulating required protocols for specific ingredients submitted to this Panel for review which have been placed in Category III.

Antimicrobial oral health care products are tested to determine the ability of an active ingredient in a product to kill an axenic population of specific organisms by the following method:

(1) *Test organisms.* (i) *Streptococcus mutans,* ATCC number 25175

(ii) *Actinomyces viscosus,* ATCC number 19246

(iii) *Candida albicans,* ATCC number 18804

(iv) *Pseudomonas aeruginosa,* (optional) ATCC number 10145

(2) *Stock cultures.* Cultures of American Type Culture Collection (ATCC) origin are subdivided and lyophilized or frozen at −25° C or lower to provide standard stock cultures for future use. The optional culture may be used if it is desirable to test a gram-negative bacterium.

(3) *Test cultures.* A stock culture of each species is first revitalized and then transferred to fresh brain heart infusion (BHI) broth, in order to initiate a battery of tests. The cultures are transferred to fresh BHI broth for two successive days following the first transfer. All incubations are to be carried out at 37° C. It is suggested that the *Actinomyces viscosus* and *Streptococcus mutans* be cultured anaerobically, the *Candida albicans* cultured aerobically. It is suggested that the candida and strepotococcus cultures be incubated for 16 to 18 hours; the actinomyces culture for 32 to 36 hours, so as to be able to compare tests from one laboratory to another.

(4) *Test medium.* Letheen broth or another inactivating medium (to eliminate carry over of active components) is prepared and dispensed in 9.9-mL quantities in unlipped culture tubes, capped with closures or plugged with cotton and then autoclaved.

(5) *Reaction tubes.* Sterile, unlipped test tubes, capped with closures or plugged with cotton, are used for mixing the cultures in the mouth rinse or mouth rinse components in the test.

(6) *Temperature of the test.* The oral health care product, as commercially available, or each active ingredient at the product concentration, in a suitable inactive vehicle, and the test culture must be brought to temperature equilibrium in a water bath at 37° C and held at this temperature throughout the test.

(7) *Test method.* (i) One milliliter of the test culture and 9 mL of the product or active ingredient (as noted above) are mixed rapidly and thoroughly. A stop-watch is started at the time of mixing.

(ii) At 1 and 2 minutes, 0.1 mL of the raction mixture is aseptically removed and inoculated into the tubes of the inactivating medium and mixed.

(iii) These tubes are incubated at 37° C for 48 hours. At this time, the entire contents of the culture tubes which exhibit no growth are aseptically transferred to 90 mL of sterile inactivating medium, to further dilute any carry-over of active ingredients(s). If upon further incubation for 1 week at 37° C no growth is detectable, the test microorganisms will be considered to have been killed by the test oral health care product or its ingredients.

(iv) As a control on the viability of the test organisms, 1 mL of the test culture is diluted in 9 mL of BHI broth and 0.1 mL of this mixture is added to inactivating medium (with no test product or ingredient) and incubated at 37° C.

(v) Replicate test samples must be done and must exhibit reproducibility.

(vi) A reference (positive) standard control is necessary to validate the test procedure by assuring the consistent susceptibility of the test organisms. Chlorhexidine digluconate, 0.2 percent in sterile water, is acceptable for this purpose.

(8) *Test in the presence of biological fluids.* Antimicrobial agents are subject to dilution with secretions in the mouth and throat. Saliva, crevicular fluid, and serum are the biological fluids of the mouth and throat which may exhibit inactivating effects on antimicrobial agents. Sterile whole human saliva, i.e., membrane filter saliva, would appear to be the ideal test mouth secretion because it is the principal oral biological fluid, but it is not recommended for use because it cannot be standardized from one laboratory to another. Sterile fetal calf serum is used instead of saliva because it possesses similar proteinaceous inactivation characteristics, few antibodies or antimicrobial components, and may be obtained commercially in standardized forms. It may be necessary to omit the addition of serum to the reference standard control, e.g., chlorhexidine, because serum, in some instances, inactivates the antimicrobial agent. The effect of serum on the product or test ingredient must be demonstrated.

The oral health care product, as commercially available, and each active ingredient at product concentrations in a suitable active vehicle are tested in the presence of a standardized biological fluid as follows:

(i) Two milliliters of sterile fetal calf serum is added to 2 mL of test organism and tested. Two milliliters of the mixture is added to 8 mL of the product or active ingredient and mixed (as noted above).

(ii) The mixture is tested as previously described under "Test method."

(9) *Evaluation.* An active antimicrobial ingredient will have passed the in vitro test if it kills all the test organisms, in the presence and in the absence of serum, within 2 minutes. Results of the test at 1 minute will be provided for information only and will not be used for comparison among products or ingredients. The 2-minute exposure time reflects the contact time of the antimicrobial product or ingredient in vivo, before it is diluted by saliva and other oral biological fluids.

b. *In vivo testing.* In vivo testing should be designed to closely approximate the clinical situations for which a product is intended to be used and to substantiate claims in the labeling that the relief of symptoms of mouth and throat infections is indeed due to an antimicrobial activity of an ingredient. A well-designed study should demonstrate that the antimicrobial effect is due to the agent itself and not to the vehicle. Control groups should receive treatment with inert vehicles which are identical in appearance, color, and consistency to the test material. A double-blind procedure should be employed to minimize bias in making observations and in reporting results. An appropriate procedure to insure the random allocation of subjects to treatment and the comparison of groups should be employed. In vivo testing, including animal and human models, should be performed prior to clinical studies.

The Panel is aware of the difficulty in conducting large-scale prospective clinical trials, and, therefore, suggests that statistical methods, such as the use of sequential designs, may be used in limiting the sample size.

The Panel is aware of the fact that some microbiologists have relied upon reduction of deposits of plaque on the teeth as an index of effectiveness of antimicrobial ingredients used in oral health care products for treating symptoms of sore mouth and sore

throat. Elsewhere in this document appears a discussion of plaque reduction and its relationship to antimicrobial activity and the fact that the Panel concludes that no correlation can be established between reduction of plaque and the relief of symptoms of sore mouth and sore throat. (See part IV. paragraph A.6. above—Evaluation of antimicrobial activity.) Likewise, the Panel concludes that there is no correlation between plaque reduction and the effectiveness of antimicrobial agents in oral health care products for prophylactic use. The Panel, therefore, does not acept data on effectiveness of antimicrobial agents in oral health care products based upon their ability to inhibit plaque formation.

(1) *Human models for treatment.* It is obvious to the Panel that no reliable, satisfactory, safe, investigational models presently exist or can be devised for producing infections experimentally in the oral cavity that simulate symptoms that would be encountered clinically for testing the effectiveness of antimicrobial oral health care products. The Panel recognizes that no single protocol or test system can possibly be devised that provides proof of effectiveness for all therapeutic applications for which OTC topical antimicrobial agents are intended. Separate protocols will have to be designed to consider individual claims or groups of similar claims and to determine such factors as the antibacterial spectrum, the duration of antimicrobial action, and the effectiveness of a product or ingredient for a particualr therapeutic indication.

(2) *Wound healing.* The Panel recognizes that the determination of the effects of an ingredient on wound healing, particularly in human subjects, is difficult. Animal models with artificially contaminated wounds have been used by some investigators. However, if animals are used, these ingredients must be further tested for this attribute in human clinical trials. There is a need for the development of procedures to determine whether or not antimicrobial oral health care products topically applied to minor ulcerations and mucosal wounds exert adverse effects and delay healing in man. The Panel suggests that such protocols and study designs should be developed in consultation with FDA.

The subjects selected for such studies should have ulcerations and other open lesions in the mouth and throat that are appropriate for testing a Category III ingredient. The Panel suggests that in designing such protocols in clinical studies the characteristics of the lesion, such as color, size, amount of exudate or purulent discharge, degree of edema, and rate of epithelization should be noted at appropriate intervals. The drug should be applied in such quantities and with the same frequency as stated in the labeling. Its effects should be compared with a control. The changes in the size, color, and appearance of a wound area can be followed by serial photographs or by planimetry or both.

3. *Selection of patients.* The final appraisal of the effectivness of a topical antimicrobial agent must be undertaken in a clinical setting under circumstances conforming to actual conditions existing in a target population for which use of the product is intended. Testing must conform to accepted ethical standards. Animal and human models may lessen the need for extensive, time-consuming, expensive clinical trials on agents that are found to be effective in model systems. The Panel, however, expects that whatever clinical studies are undertaken should be adequate to confirm the resuts of model studies. Testing of the complete formulation for effectiveness will be required to judge the importance of the vehicle in the release of the active ingredients as well as the influence that the formulation exerts on effectiveness and safety.

4. *Interpretation of data.* The recommended dose of an antimicrobial agent should induce a statistically significant reduction of symptoms or a positive amelioration of a disease process when compared with a placebo response.

Evidence of drug effectiveness is required from both in vitro and in vivo testing based upon the results of two or more independent investigators or laboratories. All data submitted to FDA must present both favorable and unfavorable results.

5. *Determination of safety.* Tests for safety must be topical and systemic. These have been mentioned elsewhere in this document. (See part II. paragraph C.2. above—Testing for recategorization of Category III ingredients.) They are specifically mentioned in more detail here due to the cytotoxic nature of many of the antimicrobial ingredients. It is known that some antimicrobial drugs that kill microorganisms may in most cases injure some cells of the host. For this reason the local effects must be defined. Also, these drugs are readily absorbed from the mucous membranes and can act systemically. Systemic toxicity is therefore an important consideration particularly when they are advocated for long-term use on a day-to-day basis for years or even over the span of a lifetime as would be the case when using mouthwash and gargle preparations.

a. *Topical safety testing.* The primary irritation potential of an ingredient following acute and subacute exposures must be determined. Special attention should be devoted to the effects on the mucous membranes of the mouth and throat.

The potential for development of topical allergic reactions following short- or long-term exposure must be determined.

The potential for development of photosensitivity must be determined.

The effect on wound healing must be determined, particularly any inhibitory effect.

The effect of subsensitivity or accumulation of an ingredient on the mucous membranes must be determined.

The above tests should be performed using each ingredient in pure form, individually, if they are in a combination, as well as the final complete formulation to judge the effect of the vehicle in the release of the active ingredients.

b. *Systemic safety testing.* The Panel requires the qualitative and quantitative determination of metabolites in biologic tissues and secretions in cases where it deems the data are essential if not available. The Panel recommends the development of adequate chemical, analytic, or bioassay techniques if not available.

The determination of the degree of absorption through the mucous membranes by measurement of blood levels is required after acute exposure as well as after chronic usage and exposure. If the product is an aerosol, adequate inhalation studies should be conducted to determine the quantity inhaled and systemic effects and accumulation in blood and tissues.

The target organ or organs susceptible to the toxic effects of the drug and the quanitity causing these effects should be determined. Toxicity should be correlated with blood levels and half-life of the drug. If a toxic effect develops, the blood levels causing such toxicity should be determined in several species. The maximal lethal dose and the minimal lethal dose and the LD_{50} should be determined in animals. Tissue distribution, metabolic rates, metabolic fate, and routes of excretion should be determined in cases where the Panel so recommends, if such data are lacking and deemed essential.

The Panel is unable to comment on the tumorigenicity, mutagenicity, or teratogenicity of the ingredients it has evaluated with the data it has available. The possibility that they do exert these

effects cannot be disregarded even though many of these drugs have been in use for many years. The Panel however, does not expect the sponsor of a product to conduct studies to obtain such data if they are not available since these involve complex studies and are conducted by the National Cancer Institute (NCI) and other agencies equipped for such investigative work.

D. Minority Report on Antimicrobial Agents

The goal of the Advisory Review Panel on OTC Oral Cavity Products was to determine if drugs used in the oral cavity and purchased over-the-counter by the consumer are safe and effective. A final report was written and, because portions of it are deficient in the opinion of a minority of the Panel, the following minority report is offered.

1. *Restrictions on the scope of investigation.* The charge of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel) was restricted to an investigation of those liquid, gel, or solid drug formulations for use in the oral cavity that were not used for symptomatic relief of colds, cough, or related upper respiratory disease. A further restriction was that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) was charged to investigate the safety and effectiveness of all oral drugs that were dentifrices, fluorides, and other antidental-plaque drugs, as well as those products used to treat oral mucosal injuries. As time passed the Dental Panel deferred consideration of the antiplaque claims. These restrictions meant that the scope of investigation of the Oral Cavity Panel was limited to the area of mouthwashes, mouth rinses, oral lozenges, gels, and other drug formulations used either to relieve symptoms of general diseases or to maintain oral hygiene.

It was an exceedingly complex problem to determine the effectiveness of mouthwashes and similar drugs, because such OTC preparations are generally not used to cure or alleviate specific oral diseases.

The antimicrobial oral cavity products, especially the antimicrobial mouthwashes, have only recently included the "antiplaque" claim in their labeling and advertising. They are used today to refresh the breath and by some consumers in an attempt to prevent the two most common and widespread diseases of the oral cavity: dental caries and periodontal disease. This use by the consumer is a recent one because of advertising and is directed toward the reduction in dental plaque by mouthwash formulations that contain antimicrobial agents.

The antiplaque activity of antimicrobial mouthwashes and mouth rinses was a parameter that the Oral Cavity Panel believed, during the first 4 years of its tenure, was a reasonable parameter to measure the antimicrobial activity of the drugs. The Dental Panel for a while considered the antiplaque claim of oral drugs, but in its later stages deferred this scope of investigation to the Oral Cavity Panel. In its last year of activity, the majority of members on the Oral Cavity Panel suddenly abandoned consideration of the antiplaque activity. The decision to abandon investigation into the antiplaque claim created a condition where none of the OTC advisory panels had jurisdiction over antiplaque claims. It may have been that the espousal of the Oral Cavity Products Panel stimulated the advance of antiplaque claims by manufacturers of antimicrobial mouthwashes. The sudden reversal of the Panel and abandonment of consideration of such claims creates an unfortunate situation in which no OTC advisory panel has jurisdiction over antiplaque claims and manufacturers of antimicrobial mouthwashes have no direction or guidelines to prove the effectiveness of their formulation in killing bacteria in the oral cavity.

2. *Guidelines to determine the effectiveness of antimicrobial mouthwashes or mouth rinses in the laboratory.* In 1977, the Oral Cavity Panel approved guidelines for the in vitro and in vivo effectiveness of antimicrobial mouthwashes. (See part IV. paragraph D.5. below—Proposal for the antimicrobial evaluation of oral cavity products.) These guidelines were established after consultation with experts in academia, in government, and in industry. The guidelines were constructed to be procedures that were in harmony with the existing body of knowledge relating to the role that bacteria play in dental caries and periodontal diseases. The in vitro procedure was based on the approved methodology employed for the general assay of antimicrobial drugs (Ref. 1). The in vivo procedure was based on reduction of plaque formation. These guidelines were intended to present general procedures that would enable drug manufacturers to reasonably demonstrate the effectiveness of antimicrobial mouthwashes.

The procedures developed by members of the Panel were intended to be guidelines, based on the present "state of the art" procedures. If advances were made in the future in the "state of the art" in either in vitro or in vivo procedures, it was expected that the newer and improved methods would be used at that time to test effectiveness of the drugs.

One consideration in designing the in vitro guidelines concerned recent evidence that in animal models, certain dental diseases involved with dental plaque have a specific bacterial component. This was reflected by the choice of *Streptococcus mutans,* ATCC number 35175, serological group C; *Actinomyces viscosus,* ATCC number 19246; and *Candida albicans,* ATCC number 18804. These test organisms are representative of the pathogenic oral bacteria and fungi. *Streptococcus mutans* and *Actinomyces viscosus* represent supragingival plaque-inhabiting bacteria that have been shown repeatedly to be caries-inducing in animal model systems, and to be associated with human dental caries (Refs. 2 through 8) and periodontal disease (Refs. 9 through 12). *Candida albicans* represents a fungus that causes oral yeast infections (Ref. 13).

The Panel considered the inclusion of anaerobic oral pathogenic bacteria, but, because of the technical difficulties involved in their culture (Ref. 14), rejected the choice. The other possible choices of oral representatives included *Veilonella alcalescens,* an anaerobic gram negative oral pathogen that was rejected because it had not been shown to cause oral diseases (Ref. 15). Spirochetes are widely regarded as being involved in periodontal disease, but they would not be suitable test organisms because they cannot be readily cultivated, if at all (Ref. 16). *Bacteroides melaninogenicus* and *Bacteroides asaccharolyticus* have been recently implicated in periodontal disease (Refs. 17 and 18). These species are obligate anaerobes and require careful and complex anaerobic culturing. The use of these two as test organisms would represent an escalation in the cost and time necessary for the in vitro testing of antimicrobials.

In view of the difficulties in cultivating oral anaerobes, the in vitro test was limited to the three test organisms, which at present, are the most odontopathic members of the supragingival plaque. It was suggested in the guidelines that *Pseudomonas aeruginosa* be employed as representative of the gram-negative oral bacteria, should that choice prove desirable (Ref. 19). These recommendations were approved by the Panel.

A recommendation, not approved by the Panel, was that chlorhexidine be used as a positive control. Chlorhexidine is the most effective in vivo plaque agent yet described (Refs. 20 through 23). A minority of the Panel recommended the use of chlorhexidine because evidence was desired that the antimicrobial mouthwashes were bioequivalent to chlorhexidine. Although chlorhexidine is not yet available for use by the public in the United States because of several problems involved with this antimicrobial agent (Ref. 24), it remains the most effective antiplaque agent, one to which all others might ideally be compared.

These guidelines for the in vitro test were suggested as pathways to a scientific evaluation of the antimicrobial activities of oral mouthwashes.

3. *Guidelines for the clinical evaluation of antimicrobial mouthwashes or mouth rinses.* The translation of the evidence obtained by in vitro testing to measure the efficacy in the oral cavity was a challenge. It became apparent to the Panel that progress to the stage of clinical trials was inevitable, given the current data base available in dental research.

The formulation of guidelines acknowledged that dental plaque, for the most part, is a microbial aggregation or clumping of bacteria on the tooth surfaces. Numerous cultural and electron microscopic studies confirm this fact (Refs. 25 through 32). Clinical investigations have demonstrated repeatedly that cessation of oral hygiene in humans results in increases in the amount and extent of dental or bacterial plaque and leads to inflammation of the oral mucosa or gingivitis (Refs. 9, 33, and 34). Once oral hygiene is reinstituted, the amount and extent of dental plaque decrease and the gingival inflammation decreases; moreover it has been demonstrated that mechanical debridement procedures designed to reduce dental plaque are essential for optimal periodontal health (Refs. 35, 36, and 37).

This relationship also existed when chlorhexidine was used as a mouthwash by human volunteers. The use of the antimicrobial mouthwash or dentifrice gel, twice daily, at a concentration of 0.2 percent of chlorhexidine gluconate resulted in a drastic reduction in gingivitis and dental caries (Refs. 38 and 39).

It has also been demonstrated that some of the quarternary ammonium compounds, cetylpyridinium chloride and benzalkonium chloride, if used as a mouthwash show plaque-inhibiting properties approaching that of chlorhexidine (Ref. 40).

This evidence, together with submissions from industry and published papers in the literature, documenting the antiplaque activity of various mouthwashes, make it reasonable to accept that reduction in dental plaque, resulting from daily use of mouthwashes, probably reduces gingival inflammation and possibly may reduce dental caries (Refs. 41 through 49).

The Panel at first accepted this principle and recommended the clinical guidelines for antimicrobial tests based on plaque reduction. The four methods used to grade plaque were:

The Quigley Hein method (Ref. 50) including the Turesky modification (Ref. 51).

The Loe and Silness method (Ref. 52).

The Schick-Ash method (Ref. 53).

The Navy scoring method (Ref. 54).

They were freely accepted by the Panel.

At the 27th meeting, the next to the last meeting, of the Panel on August 14, 1979, the guidelines, previously accepted, were abandoned.

It is the opinion of this minority that a set of guidelines are necessary to determine the effectiveness of a drug. It may have been that the majority of the Panel went too far in trying to formulate an acceptable testing method rather than a set of guidelines. Their reasons for abandonment of these guidelines are not persuasive.

Their reasons are as follows:

The species selected for the in vitro tests were not representative; anaerobes were omitted and a gram-negative bacterium was optimal.

A reduction in dental plaque biomass does not necessarily result in a benefit to the consumer.

A reduction in plaque biomass does not necessarily mean a reduction in plaque bacteria.

Subjective methods of assessment of dental plaque are not valid.

The daily use of oral mouthwashes may cause a shift in the oral flora that may result in a proliferation of pathogenic bacteria.

The minority of the Panel dissents from these five assertions:

As was discussed previously, the oral bacteria species chosen for the in vitro tests were representative of the three leading oral pathogens. (See part IV. paragraph D.2. above—Guidelines to determine the effectiveness of antimicrobial mouthwashes or mouth rinses in the laboratory.) A fourth species, *Pseudomonas aeruginosa* was suggested as an optional representative of the gram-negative bacteria.

It would have been sufficient to select only one test organism to demonstrate antimicrobial activity because bacterial susceptibility differences to antimicrobial chemicals are usually slight. Three test organisms that were selected, the two facultative anaerobic gram-positive bacteria and the fungus, covered most of the susceptibility differences to antimicrobial activity.

As was discussed elsewhere, reduction in plaque biomass in humans who have temporarily abandoned oral hygiene practices results in reduction of gingivitis. (See part IV. paragraph D.3. above—Guidelines for the clinical evaluation of antimicrobial mouthwashes and mouth rinses.) Reduction in plaque then certainly reduces the disease potential by prophylactically reducing the visible periodontal disease, and if the antimicrobial mouthwash can penetrate the gingival crevice, it may reduce the hidden periodontal disease. It most certainly does act prophylactically by reducing the pathogenic challenge to the periodontal tissues by killing a minimum number of oral microorganisms located adjacent to and below the margins of the gingiva.

Tens of millions of United States citizens suffer from one mild form of periodontal disease, namely gingivitis caused by the presence of dental plaque. Most of these individuals are not treated for this disease and only toothbrushing, flossing, and the use of antimicrobial mouthwashes prevent in many of these individuals the extension of the gingivitis to the more severe forms of periodontal disease. The action of the mouthwashes are of short duration but this temporary reduction combined with other oral hygiene techniques benefits the consumer.

This minority of the Panel recommends that those antimicrobial mouthwashes or mouth rinses which have demonstrated the ability to reduce dental plaque and reduce or prevent gingivitis or do both be approved in Category I and be allowed the claim "temporarily reduces gingivitis-causing dental plaque when used together with toothbrushing and flossing."

There are two kinds of measurements that have been used to assay plaque biomass. These are area measurements and plaque weight measurements.

The area measurements, such as the Quigley-Hein system (Ref. 50), is a method for assessing the effectiveness of various procedures in removing dental plaque from different surfaces of the teeth. The individual takes a disclosing rinse or is subjected to a fluorescing light which will disclose

plaque on the tooth surface. The buccal (cheek) or labial (lip) surfaces are inspected and a numerical value is given depending on how much of the tooth surface area is covered by the disclosed plaque. Area measurements are subjective to a degree since they require evaluation by an examiner, and they are somewhat inexact because they may not distinguish between thin films or thick films of dental plaque.

Weight measurements of dental plaque, on the other hand, are useful in determining whether a non-mechanical agent is exerting some effect on the amount of dental plaque during a specific period of time. The method selects certain tooth surfaces and the dental plaque is thoroughly and carefully removed. The plaque is thoroughly and carefully removed. The plaque samples may be placed in preweighed capsules, to minimize water loss, and then weighed. Another method is to weigh the sample immediately; or a third method is to dry the samples, eliminating water content differences, and then weigh the samples. In this manner, the effect of an antimicrobial mouthwash can be analytically and objectively measured and a decrease can be analytically and objectively measured and a decrease in the mass of dental plaque formed during a specific time period quantified.

When weight measurements are done, it has been demonstrated that there is a reduction in the number of plaque bacteria on the tooth surface. Plaque is more than 80 percent bacteria (Ref. 56). A 100-percent reduction in dental plaque on the tooth surface would mean a more than 80-percent reduction in plaque bacteria on the same surface.

One of the bases for the decision of the majority of the Panel that a reduction in plaque biomass does not necessarily reflect a reduction in plaque bacteria was a comment by a consultant to the Panel who said that "it may be possible to reduce biomass without killing plaque bacteria." The consultant failed to indicate that this was a theory that had not yet been demonstrated to function in the human oral cavity. He cited three possible mechanisms for this nonantimicrobial plaque reduction:

Fluoride—Recent evidence suggests that the primary action of fluoride mouth rinses is antimicrobial (Ref. 57).

Phytate—Phytate acts as a chelater, removing calcium from the plaque environment. The consultant was experimenting with phytate at the time, but had not demonstrated that it removed dental plaque in the human oral cavity.

Dextranases—Dextranases are supposed to break up the extracellular glucans which consist of less than 2 percent of the dental plaque. Dextranases have been shown to be ineffective in human clinical trials (Refs. 58, 59, and 60).

There is no evidence to the knowledge of this minority that a nonmechanical agent may reduce dental plaque without reducing plaque bacteria.

There is no justification for the abandonment of the in vivo guidelines, especially since they are guidelines. The present "state of the art" is that area measurements of plaque tend to be somewhat subjective and inexact; while weight measurements are objective and more accurate but tedious. As the "state of the art" progresses there will be less tedious and more accurate methods of plaque assessment. These methods will fall within the spirit of these guidelines. The presently available methods while not ideal are adequate to assay reductions in plaque.

The possibility of a shift of the oral flora with long-term and daily use of an antimicrobial mouthwash does have a scientific basis (Ref. 6). In a year-long study on a small number of humans who used a 0.5-percent chlorhexidine-containing gel dentifrice, there was a reduction in the proportion of the more pathogenic (cariogenic) *Streptococcus mutans* and an increase in the less pathogenic *Streptococcus sanguis* from 0.002 percent of the flora prior to treatment, to 34 percent of the flora after treatment. This shift was beneficial for the subjects. None of the other pathogens, staphylococci, streptococci, gram-negative rods, or yeasts, increased.

There are no reported cases in the literature of pathology as the result of a shift in oral bacteria following daily and long-term use of antimicrobial mouthwashes.

There is as yet no evidence that a shift in oral flora, if it occurs as a result of the long-term use of mouthwashes, will result in a pathological condition in the oral cavity.

4. *Approval of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride as Category I ingredients for safety and effectiveness for use on the oral and pharyngeal mucous membranes.* On August 14, 1979, at the 27th, next to last, meeting of the Panel, the Panel by a vote of four votes approving and two abstaining reversed its previous position (Category I) and changed the categorization of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride from Category I to Category III for both safety and effectiveness for use on the oral and pharyngeal mucous membranes. The majority of the Panel arrived at this decision because their previous vote approving these three as Category I was based on experiments suggested by the in vivo and in vitro guidelines, which the Panel had abandoned. Their concern for safety was based on a lack of long-term studies on the carcinogenicity, teratogenicity, and pathology resulting from a shift in the oral flora. Their loss of faith in the effectiveness of these three ingredients was not as a result of new evidence demonstrating that they were not effective, but rather on their loss of faith, after 4 years, in the in vitro and in vivo guidelines which they previously had approved and then abandoned.

On December 14, 1979, at the 28th meeting, the last meeting of the Panel, a vote was taken on a motion to approve cetylpyridinium chloride, domiphen bromide, and benzethonium chloride as Category I for safety and effectiveness in oral health care for use on the oral and pharyngeal mucous membranes. There were three votes for and four votes against the motion. The following is the minority's point of view.

There have been a number of reports published in the dental literature demonstrating the clinical effectiveness of these three antimicrobial agents in reducing dental plaque (Refs. 41, 42, and 45 through 49). A journal article must undergo review by peers before it is accepted for inclusion in a scientific publication. Publication in the literature indicates scientific approval. The antiplaque claim of cetylpyridinium chloride, domiphen bromide, and benzethonium chloride can be said to be accepted by the scientific community to be effective in reducing bacterial plaque. Bacterial plaque, the scientific community agrees, is the cause of dental caries and one of the possible causes of periodontal disease.

The following is a direct quote from an article by Johnson and Rozanis (Ref. 62):

"Quarternary Ammonium Compounds"

Because the daily use of commercial mouthwashes to 'sweeten one's breath' is a common practice in many parts of the world, their potential as a valuable public health measure in the control of dental disease is enormous. Studies on two commercial brands containing quarternary ammonium compounds have shown some beneficial effects in short-term trials. Cetylpyridinium chloride and domiphen bromide have been studies, and claims of a reduction in plaque and gingival indices have been made. When cetylpyridinium chloride was tested, there was a decrease in plaque accumulation but no significant reduction in the gingival index. Perhaps the lack of gingival effect, despite the reported inhibition of supragingival plaque, is due to the fact that those bacteria effected are not the ones involved in the initiation and

progression of gingivitis or the agents are not carried subgingivally where they can "attack" those bacteria that are possibly more intimately related to the development of the disease.

Gjermo, Baastad, and Rolla (Ref. 48) demonstrated a rather good in vitro inhibition of plaque formation with a 0.2-percent solution of benzalkonium chloride. However, when tested clinically, four of the five volunteers developed painful desquamative lesions of the oral mucosa and the investigators discounted it for general use. Compton and Beagrie (Ref. 49) gained a 42-percent reduction in plaque, but not statistically significant decrease in gingivitis, with benzethonium chloride.

Aside from the elimination of benzalkonium chloride as a safe and effective mouthwash, cetylpyridinium chloride, domiphen bromide, and benzethonium chloride have been shown in the above excerpt to be effective in reducing dental plaque in short-term studies while not necessarily reducing the index of gingival inflammation. Their therapeutic value may be questioned, but their prophylactic effectivity is unquestioned.

These three are effective and should be reinstated in Category I. The minority of the Panel would also suggest that other mouthwashes that meet the criteria of the guidelines be approved as Category I for effectiveness for use on the mucous membranes of the mouth and throat.

5. *Proposal for the antimicrobial evaluation of oral cavity products*—a. *Introduction of the problem.* Standard methods are needed to determine the effectiveness of antimicrobial agents used in the oral cavity. The antimicrobial agents may be natural or synthesized chemical elements, compounds or mixtures of compounds used in antiseptics, disinfectants, astringents, gargles, lozenges, troches, or mouthwashes. The antimicrobial activity is the property of antiseptics or disinfectants to be assayed.

The present method of determining the relative antimicrobial efficiency of any of the chemical disinfectants is to compare them to another disinfectant. One of the official tests used, at present, to compare disinfectants is the phenol coeffficient test. This test is a standardized technique of determining the antimicrobial power of a given chemical compound as compared to that of a standard disinfectant, phenol.

The phenol coefficient of a chemical compound is a numerical value presumed to indicate whether, and to approximately what extent, a chemical compound is a better or poorer compound than phenol. This numerical value is obtained from a ratio of the minimal sterilizing concentration of a given compound as compared to the minimal sterilizing concentration of phenol tested under standard conditions. In the official tests used by FDA and other regulatory agencies of the U.S. government, the following standard procedure is followed. A chemical disinfectant is diluted to given concentrations. The standard disinfectant, phenol, is similarly diluted. A standard concentration of a designated bacterial culture is added. The most dilute concentration capable of killing the bacterial culture after 10 minutes of exposure is the end point for the given chemical disinfectant. Phenol is tested under identical conditions. The end point dilution of phenol is divided into the end point dilution of the given disinfectant and the ratio obtained.

In the official phenol coefficient test, the test bacterial cultures that are commonly employed include *Salmonella typhosa,* a representative of a pathogen of the intestinal tract, and *Staphylococcus aureus,* typical as a major environmental source of wound infection and some spore-forming bacteria. Occasionally, other test organisms are utilized.

The phenol coefficient provides a reasonable index for comparing various phenol derivatives which exhibit kinetics and modes of action similar to phenol. It is less than satisfactory for other antimicrobial agents which may differ in their concentration action curves, temperature coefficients, and their susceptibility to neutralization by their immediate environment. Consequently, many variations of the phenol coefficient test have been developed to evaluate the antimicrobial potency of nonphenolic compounds. These variations depend upon a sterility end point.

Microbiologists agree that this end point of sterility is questionable and a more accurate assay of antimicrobial activity would be on the rate of killing of bacteria by the chemical. The rate of killing or reaction velocity constant is exponentially related to the concentration of the disinfectants according to the following expression: $K=C^nt$, where K = the reaction velocity constant of killing, C = the concentration of the chemical, n = a constant characteristic for each chemical, and t = the time of contact.

It would be difficult technically to determine the rate or kinetics of killing; as a result, the tests utilizing the less accurate and less precise sterility end point are more commonly employed.

Generally, assays for the effectiveness of antimicrobials are made by testing known concentrations of antiseptics or disinfectants against one or more test microorganisms and comparing it to a standard or control.

b. *Proposal for an in vitro evaluation of antiseptics or disinfectants used in the oral cavity.* Two factors are necessary for the in vitro assay of the antimicrobial or disinfectants, and these are typical test microorganisms and a standard disinfectant.

(1) *Test microorganisms.* Those microorganisms known to cause disease in the oral cavity should be used as test cultures to assay the potency of oral products.

The following strains are suggested as test microorganisms:

(a) *Streptococcus mutans* is one of the gram-positive cocci microorganisms implicated in the development of dental caries. It has been directly associated with active carious lesions and in the formation of dental plaque. It is typical of the other oral streptococci. Presumably, any disinfectant that kills *Streptococcus mutans* would be equally effective against any of the other oral streptococci.

(b) *Actinomyces viscosus* is a gram-positive filamentous rod recently implicated in the triggering of experimental periodontal disease. This bacterium is typical of the filamentous bacilli found in dental plaque. If an oral product has any therapeutic value, it should inhibit this class of oral microorganism.

(c) *Candida albicans* is a yeast found in the oral cavity. It may be more difficult to inhibit than *Streptococcus mutans* or *Actinomyces viscosus.* It is involved in oral yeast infection including denture sore mouth. This organism is typical of the oral fungi.

Other test organisms may be employed as it becomes appropriate. Gram-negative bacteria constitute a minority of the oral flora, and most are anaerobes which present technical problems in cultivation. Gram-positive bacteria and yeasts present greater challenges to disinfectants than do the gram-negative bacteria.

Viruses must be cultured in cells in tissue culture and present a greater laboratory hazard and technical difficulties. Once the hepatitis virus B (Dane particle) is routinely cultured, it could be used by virucidal testing.

(2) *Standard disinfectant or antiseptic.* Ideally, a proven effective disinfectant should be used as the standard. At present, there appears to be only one compound that will inactivate *Streptococcus mutans* and other caries-inducing experimental caries, and retard or reverse incipient

periodontal disease. This disinfectant is chlorhexidine, an antibacterial bisbiguanide. Its chemical name is 1,6-*DL*-(4-chlorophenyldiguanido) hexane. It has a large antimicrobial range against a wide range of bacteria. It is being used in Europe as a topical antiseptic and as a disinfectant in genitourinary diseases as well as diseases of the eye and oral cavity. It is a potent antibacterial commercially available in Europe as the gluconate or acetate salt.

Chlorhexidine is also antimicrobial to other oral streptococci, *Staphylococcus arueus, Escherichia coli,* and *Candida albicans.* It is inhibitory to a wide variety of microorganisms, but is not sporocidal, except at temperatures approaching the boiling point of water. Viruses do not appear to be susceptible to the action of chlorhexidine.

The possible mode of action of chlorhexidine is to exert a lethal action on the cell surface of microbial cells by disorganizing permeability barriers and coagulating the cytoplasmic contents.

This disinfectant, chlorhexidine, would be an ideal standard. It is effective at 1 to 2 percent dilutions and will inhibit the three proposed test organisms: *Streptococcus mutans, Actinomyces viscosus,* and *Candida albicans.*

The chlorhexidine "coefficient test" would be used to compare any oral product against chlorhexidine. The ratio obtained would demonstrate the relative efficiency of a product as compared to chlorhexidine.

c. *Proposal for the in vivo evaluation of antiseptics or disinfectants used in the oral cavity.* An in vivo method should measure parameters that will result in improved oral health.

Three parameters are used at present:

(1) Reduction in the quantity of dental plaque.

(2) Reduction in the numbers or kinds of microorganisms in the saliva.

(3) Reduction in the numbers or kinds of microorganisms in dental plaque.

The reduction in the quantity of dental plaque is determined by the use of disclosing agents or stains. The teeth are stained with dyes, or chemical disclosing agents, and examined under white light or ultra-violet light. Photographs are taken, and the areas colored by the light or the stain are mapped, measured, and compared to the total area of the teeth. This procedure is used before and after the use of a disinfectant.

The defects in this method are that it is laborious, tedious, and difficult to reproduce. It is time consuming, but its greatest defect is that it is inaccurate.

The reduction in the number or kinds of microorganisms in saliva is another measurement of the efficacy of oral disinfectants. Saliva is only one of the sites of the microbial flora.

The late Dr. Henry Scherp compared this method to a determination of the bacterial content of the soil at the headwater of the Mississippi in Minnesota by measuring the river water at New Orleans. It does not accurately describe what is occurring on the tooth surface nor in the gingival sulcus areas where most dental disease occurs.

A more accurate general in vivo method that reflects microbial changes on the tooth surface or in the gingival sulcus is one in which plaque material is quantified for reduction in the plaque flora.

Plaque is removed from designated areas on the tooth surface or gingival crevice. It is weighed to obtain a value per milligram of plaque. It is sonicated carefully to disperse the plaque. Isolated species may be identified and quantified, or groups may be quantified. In this manner reductions in microbial counts in areas important in dental disease can be determined.

There are many variations on this in vivo technique. One such variation developed which has been used to quantify microbial reduction on the tooth surfaces by mouthwashes is the agar replica method.

In the agar replica method, an impression of the patient's teeth is taken before and after use of the mouthwash in irreversible hydrocolloid. The bacteria on the surface of the plaque are transferred to the impression material. Bacterial culture medium is poured aseptically into the hydrocolloid impression. The bacteria are transferred from the impression material to the surface of the agar. The agar shrinks slightly and is removed from the impression. A model of the patient's teeth and gingiva are obtained with colonies of bacteria growing in the exact sites they occur in the mouth. These colonies are counted after incubation and by comparing the before and after use of the mouthwash, one can quantify the reduction in microorganisms colonizing the tooth surface or upper portion of gingival sulcus.

One of these in vivo methods should be adopted, as is appropriate, to measure the antimicrobial activity of oral cavity products. This minority of the Panel suggests it be either the direct sampling from plaque and counting microorganisms or one of the variations such as the agar replica technique.

In summary, this minority of the Panel makes the following recommendations:

It is recommended that an in vitro test utilizing chlorhexidine, an effective oral disinfectant, as a standard be used and all other oral products be compared to this standard. This will serve to give an estimate of relative antimicrobial potency of oral products.

In the above test, three easily cultivable and identifiable oral organisms, *Streptococcus mutans, Antinomyces viscosus,* and *Candida albicans,* can be used as test organisms in the in vitro test.

It is recommended that, once an oral product shows promise for relative antimicrobial activity in the in vitro test, it be tested by an in vivo method. A direct sampling of dental plaque from designated areas on the tooth and gingival sulcus or one of its variations should be used.

These two approaches will make possible an accurate evaluation of the antimicrobial properties of oral products.

6. *Additional methodology for evaluating antimicrobial active ingredients*—a. *Introduction.* The objective of this report is to present a protocol of test methods which will determine the effectiveness of antimicrobial agents used in the oral cavity. These antimicrobials are antiseptics, disinfectants, astringents, gargles, lozenges, troches, or mouthwashes which are presently being sold without prescription (OTC) for use by the general public in the oral cavity. The property of these products to be evaluated in this report is their relative antimicrobial activity.

The variety of antimicrobial agents recommended for use in the oral cavity is great. No single bacteriological test method for evaluating all agents can be expected to be adequate for all. The problem of testing these agents should be resolved with the following considerations:

(1) The development of a method which will provide meaningful results.

(2) The precise application of this method.

(3) The accurate interpretation of the results based on adequate controls and a precision sufficiently accurate so that the results can be reproduced uniformly.

b. *Definitions*—(1) *Antimicrobial.* Any physical agent or chemical that destroys or inhibits the growth of any microorganism or virus.

(2) *Antiseptic.* A substance that opposes sepsis, putrefaction, or decay by inhibiting the growth or action of microorganisms or viruses or destroying them. This term is used especially for agents applied to living tissue. Mouthwashes or gargles can be called antiseptics only if they destroy microorganisms during their period of

contact in the dilutions recommended for use.

(3) *Disinfectant.* An agent that frees from infection. It is usually a chemical agent which destroys harmful microorganisms or viruses, but not usually bacterial spores.

(4) *Germicide.* A term used interchangeably with "antiseptic" or "disinfectant" but one that implies that all vegetative (non-sporing) microorganisms are destroyed.

c. *Methods*—(1) *In vitro evaluation of antiseptics or disinfectants used in the oral cavity.* Oral antiseptics or disinfectants which are applied for a short time as in gargles, sprays, or mouthwashes are tested by the following methods:

(i) *Test organism. Streptococcus mutans,* strain NCTC 10449.

(*a*) *Medium.* Calf brains, infusion from, 200 g; beef heart, infusion from, 250 g; proteose peptone, 10 g; bacto-dextrose, 2 g; sodium chloride, 5 g; disodium phosphate, 2.5 g.

This medium is brain heart infusion broth (BHI). Thirty-seven grams of the BHI is dissolved in 1,000 mL distilled water. Ten milliters of BHI broth is added to 20 x 150 mm unlipped test tubes, plugged with cotton and sterilized in the autoclave in 15 pounds per square inch (lb/in^2) pressure at 121° C for 30 minutes. The final reaction of the medium will be pH 7.4.

(*b*) *Stock culture.* Each stock culture of *Streptococcus mutans* is transferred on agar slants of BHI twice a month and stored at refrigerator temperatures.

(*c*) *Test culture.* The test culture is prepared by transferring from the agar slant stock culture into 10 mL of the above broth medium and transferred and incubated at 37° C for 16 to 18 hours. This is done for 3 consecutive days to prepare the test culture.

(*d*) *Medication tube.* Unlipped test tubes 25 x 150 mm plugged with cotton and sterilized in the hot air oven at 170° C for 1.5 hours are used for mixing the cultures with the antiseptic or disinfectant in the test.

(*e*) *Temperature of the test.* The antiseptic and the test culture must be warmed in a warm bath at 37° C and held at this temperature during the period of the test.

(*f*) *Inoculation loop.* A 4-mm loop of platinum wire U.S. No. 23B and S gauge, 0.5 to 3 in long set in a suitable holder such as an aluminum or glass rod 0.5 cm in diameter is used to transfer the antiseptic culture mixture in a medication tube to 10 mL of the sterile broth in the subculture tubes. The loop and rod are flamed before each transfer which is made under aseptic conditions.

(*g*) *Incubation.* The subcultures are incubated at 37° C for 48 hours.

(*h*) *Dilution.* Any series of dilutions which may be required are made in sterile distilled water under aseptic conditions or the antiseptic may be tested at the dilution suggested by the manufacturers.

(*i*) *Methods of conducting tests.* Five milliliters of the antiseptic in the appropriate dilution is placed into sterile 25 x 150 mm tubes and warmed to 37° C in a water bath. The 16–18 broth culture of the test organism (and culture) after vigorous shaking is allowed to warm in the same water bath for 5 minutes. Five-tenths milliliters of this culture is removed by the means of a 1 mL graduated pipet and added to 5 mL of the antiseptic and mixed by slight agitation. Transfers are then made from the mixture of culture and antiseptic into 10 mL of sterile broth by the means of the sterile 4-mm loop at intervals of 30 seconds, 1, 2, and 5 minutes. These transfer tubes are then incubated at 37° C for 48 hours. At the end of the incubation period, these broth tubes are observed for evidence of growth.

The information desired from this method is the concentration of the germicide required to kill *Streptococcus mutans* under the conditions of the test within 5 minutes as compared to a standard or control agent. This agent is chlorhexidine, a compound shown to be effective against plaque bacteria. If the preparation does not kill without any comparison within 5 minutes, it has been considered not sufficiently germicidal to be classified as an antiseptic for use in the oral cavity.

Those preparations that do pass this test within 5 minutes can be then compared to chlorhexidine for their relative efficiency. In this test, 1 percent chlorhexidine is the germicide which is commonly considered to have some antiseptic clinical value to oral microorganisms to kill within 5 minutes. In the interest of fairness, if the concentration suggested by the manufacturer of the disinfectant is below or above 1 percent, it may be suitable to employ the same concentration of chlorhexidine as the recommended concentration of the antiseptic. For example, if an antiseptic is to be used at 0.5 percent, then chlorhexidine would be diluted to a 0.5-percent concentration. If the antiseptic failed to kill the test organism at 0.5 percent, but did kill at 2 percent, it would be judged to be 25 percent as effective as chlorhexidine.

The principal value of this method would seem to be that of determining the relative germicidal levels of oral antiseptics and disinfectants intended to provide contact germicidal action.

(ii) *Confirming tests.* There is always the possibility that enough of the germicide may be carried over into the subculture broth to inhibit the growth of test organisms, and false negative results may often occur. For this reason, it is necessary to determine whether the inhibitory concentration of the germicide is present in the broth.

The subculture is made by reinoculating these tubes into fresh 24-hour broth culture of the test organism by means of a sterile loop and reincubating at 37° C for 24 hours. If growth occurs after this inoculation, it means that no inhibitory action has occurred and that failure of growth during the first incubation shows that the test organisms have been killed. In case no growth occurred after the second inoculation, the test is repeated using 250 mL of broth in a flask in place of the 10 mL to avoid inhibitory reaction of the antiseptic to the subculture.

It may be that this germicidal action of the oral antiseptic would not be the same in applications in vivo as mouthwashes and gargles where the concentration would be reduced in actual application by the saliva and other body secretions, and the active ingredient would be exposed to the potentially inactivating effects of those same secretions. The details of the procedures here are, however, sufficiently flexible so that application dilutions and organic inactivating materials can be simulated with some degree of success. It is, therefore, suggested that if an oral germicide passes this stringent test, it should be tested in the presence of human saliva before it can be recommended in the oral cavity.

(iii) *Tests in the presence of saliva.* One milliliter of whole human saliva that has been sterilized by filtration through a membrane filter (e.g., Millipore) with a diameter of 0.45 mm is added to the modified test described above. This gives an equivalent further dilution of the antiseptic or disinfectant as well as the control disinfectant (chlorhexidine). In this manner a germicide can be screened for oral use (with saliva) for use as a mouthwash or gargle.

(*a*) *Test organism. Actinomyces viscosus,* strain ATCC 19246.

The same procedures as followed with *Streptococcus mutans* will be followed with *Actinomyces viscosus* except that 24-hour cultures of test organisms are used.

(b) *Test organism. Candida albicans,* strain ATTCC 18804.

The same procedures are followed except the culture media for this yeast is malt extract broth. Fifteen grams of Bacto-male extract broth is dissolved in 1,000 mL of distilled water. This medium is placed in tubes as described above and autoclaved for 15 minutes at 15 lb/in^2 pressure at 121° C. The final reaction of this medium will be pH 4.7. This medium is used in place of the BHI for the propagation of the test yeast. A 24-hour culture of this yeast is preferred to test the fungicidal action of the germicide. The tests are conducted as above.

(iv) *Gram-negative testing.* If it is necessary to test a gram-negative organism, then *pseudomonas aeruginosa,* strain ATCC 10145, is used. The above procedures are followed except culture medium.

Medium. Beef extract 5 g, peptone 10 g, sodium chloride 5 g are added to 1,000 mL of distilled water. Boil for 30 minutes to dissolve, adjust the pH to 6.8 with normal sodium hydroxide or saturated aqueous sodium carbonate (Na_2CO_3). Boil for 10 mnutes and then filter through paper and make up to original volume. Add 10 mL to the 20 x 150 mm unlipped test tubes, plug with cotton and sterilize in an autoclave at 15 .b/in^2 pressure at 121° C for 30 minutes. This is nutrient broth and can be purchased as nutrient broth. The final pH should be adjusted to 7.4. The same procedure as described above is used for this with 24-hour cultures of the test organism.

(v) *Summary of in vitro tests.* (*a*) Modified chlorhexidine coefficient tests using three test cultures.

(*1*) *Streptococcus mutans.*

(*2*) *Actinomyces viscosus.*

(*3*) *Candida albicans.*

(*4*) If necessary, *Pseudomonas aeroginosa.*

(*b*) Subcultures of above.

(*c*) Modified chlorhexidine coefficient test with 1 mL of sterile saliva.

(2) *In vivo evaluation of oral antiseptica and disinfectants*—(i) *Indroduction.* The efficacy of an oral antiseptic or mouthwash can be best evaluated by its ability to kill microorganisms in the oral cavity. As mentioned in the original proposal, the reduction in number of microorganisms in dental plaque per given weight of dental plaque seems to be the most accurate method to describe the germicidal properties of agents in the oral cavity. Killing of microorganisms. in saliva is inaccurate, and the germidical action on soft tissue is inconsistent. Two methods are proposed:

(*a*) *The reduction of microorganisms in plaque on disignated tooth surfaces in human volunteers.* Plaque is removed from designated areas on the tooth surface or gingival crevice. Prior to the use of the antiseptic, this may be done on every other tooth. For example, it maybe the facial area of the right central incisor, the buccal area of the right canine, the buccal area of the second premolar, and buccal area of the second molar together with a sampling from the corresponding gingival crevises. The plaque can be removed with a standard periodontal spoon, and the plaque is immediately placed in a preweighted gelatin capsule. Immediately after collection, the capsule is weighed and amount of plaque calculated. The capsule and its contents are aseptically homogenized in 5 mL of trypticase-soy broth. One milliliter of the homogenized plaque material is then added to 9 mL of sterile phosphate buffer. The dilution is mixed, and 1 mL of this dilution is then transferred to a second tube containing 9 mL of phosphate buffer (pH 6.8). This is continued for 8 more tubes until a dilution of 10^{10} is obtained.

One milliliter of each dilution is then placed in sterile standard petri dishes. This is done in triplicate so there are three petri dishes each containing 1 mL of each dilution. Over this dilution in each tube is poured 20 mL of tripticase-soy agar which has been melted and cooled to 45° C. The petri dishes are gently agitated in order to achieve a homogenous mix. These are appropriately labeled and then incubated for 48 hours in an inverted position at 37° C.

After incubation the plates are removed and the number of colonies on each plate counted. Any appropriate counting method may be used. Only those plates having between 30 and 300 colonies are counted, and the number of microorganisms per milligram of plaque is calculated. For example, if 10 mg of plaque were collected and then diluted completely, the number of milligrams per 20 mL culture medium means there was 0.5 mg per mL. The number of microbial colonies, for examplke, at the 10^6 dilution may be 40. This means that there were 80×10^6 (80,000,000) microorganisms per milligram of plaque.

The human volunteer then uses the mouthwash, gargle, or other oral antiseptic as directed by the manufacturer. The mouth is rinsed with sterile saline to remove all traces of residual antiseptic. Then plaque is collected from those teeth in the same quadrant that were not sampled before use of the mouthwash. The right lateral, first premolar, first molar and third molar may be sampled. The sample of collected plaque again is weighed and diluted as described above. The dilutions are plated and counted. For example, if now there are only 40×10^5 microorganisms per milligram (4,000,000) of plaque, then a reduction of 76×10^6 (76,000,000) was obtained by use of the mouthwash.

If a relative efficiency is necessary, then the same dilution of chlorhexidine could be tested in human volunteers against the mouthwash, and the relative efficiency could be determined using the above method simply by comparing the numbers reduced by the antiseptic against the control chlorhexidine.

The method described above is tedious, but new methods have been developed to do this rapidly, and instrumentation using laser counting has been developed in order to rapidly count colonies on the bacterial plates. This method is tedious, but would give an accurate general in vivo method that will reflect changes on the tooth surface or in the gingival crevice.

The methods for counting bacteria in the plates are varied. They can range from counting on a Quebec Colony Counter manually to the various mechanical counters available in microbiological laboratories.

(*b*) *Agar replica method.* The principle of the agar replia method is that microorganisms on the surface of teeth in plaque can be transferred to the surface of a dental impression material taken of the entire dentition. The next step is to pour up dental impression bacteriological agar culture media. The bacteria are now transferred to the surface of the agar model. The agar model is incubated, and the microbial colonies can be seen growing in the exact site that they occur in the mouth.

The patient rinses his/her mouth with sterile distilled water. A dental impression is taken in irreversible hydrocolloid. Perforated impression trays are used and Jeltrate®, an irreversible hydrocolloid containing little fluoride, is used as the impression material. It is mixed up, the surface of the material is washed, it is placed over the patient's teeth, and an impression is obtained of the patient's teeth. The impression material is carefully placed and removed so that a minimum streaking of dental plaque would occur.

The impression are boxed in wax and immediately poured with a fortified selective agar medium. The medium is melted and then cooled to 47° C so that it would solidify on contact with the hydrocolloid. The poured impressions are chilled, adn the agar medium model is carefully removed from the impression material.

At present two selected media have been used. The first is a modification of the formula of Rogosa, Mitchell, and Wiseman (Ref. 63). It consists of a

lactobacillus-selective broth containing brom cresol green, .02 g/L and 3 percent fortified agar (Ion agar #2). The pH of the media is adjusted to 5.5 with lactic acid. Agar models obtained using this impression are incubated anaerobically at 37° C for 48 hours.

A second selective media used for the isolation of oral yeasts is Sabouraud's dextrose broth containing penicillin, 20 units per mL; cyclohexamide, 0.5 mg/ml; streptomycin, 40 mg/mL; and 3 percent fortified agar. Agar models utilizing this media were incubated aerobically at 30° C for at least 72 hours.

These two media select only the lactobacillus in the first or the yeast in the second. As other selective media begin to be developed, they can be utilized to identify certain microorganisms. If total counts are desired, then media such as trypticase-soy or blood agar can be utilized to obtain those microorganisms which will grow on this media.

Agar models are obtained before the use of the mouthwash as described. The mouthwash is then used as recommended by the manufacturer, and models are taken again a second time. Colonies are then mapped on both models at the site. A disappearance of a colony from a certain site can be the result of the use of the mouthwash. The number of colonies that disappear will give evidence of the efficacy of the mouthwash in removing those microorganisms that are chosen by the experimenter. In this way the action on specific microorganisms, or, in the case of the blood agar medium, total microorganisms, can be determined, although not as accurately as the first method.

If a relative effectiveness is desired, again the concentration of the antiseptic to be tested can be compared to the same concentration of chlorhexidine, and a relative efficiency of killing as demonstrated by the agar replica method can be obtained.

d. *Discussion.* Two methods of evaluating the efficiency in vivo of the action of mouthwashes, gargles, and other oral antiseptics have been described. These are two suggested methods and are probably the best ways to obtain information as to the relative efficiency of the oral antiseptics in killing microorganisms in the mouth. Other methods such as saliva counts and scraping of the buccal tissue are less satisfactory and give less accurate and inconsistent evaluation. It should be noted that these are protocols of methods to be used and merely demonstrate the principles that counts in plaque are to be reduced by the antiseptic, and these are two methods suggested.

References

(1) Block, S. S., "Disinfection, Sterilization and Preservation," Lea and Febiger, Philadelphia, 1977.

(2) Keyes, P. H., "Research in Dental Caries," *Journal of the American Dental Association,* 76:1357–1373, 1968.

(3) Keyes, P. H., and H. V. Jordan, "Factors Influencing the Initiation, Transmission, and Inhibition of Dental Caries," *in* "Mechanisms of Hard Tissue Destruction," edited by R. F. Sognnaes, American Association for the Advancement of Science, Washington, pp. 261–283, 1963.

(4) Jordan, H. V., and B. F. Hammond, "Filamentous Bacteria Isolated from Human Root Surface Caries," *Archives of Oral Biology,* 17:1333–1342, 1972.

(5) De Stoppelaar, J. D., J. van Houte, and O. Backer Dirks, "The Effect of Carbohydrate Restriction on the Presence of *Streptococcus Mutans, Streptococcus sanguis* and Iodophilic Polysaccharide-Producing Bacteria in Human Dental Plaque," *Caries Research,* 4:114–123, 1970.

(6) Gibbons, R. J., "Bacteriology of Dental Caries," *Journal of Dental Research,* 43:1021–1028, 1964.

(7) Krasse, B., et al., "The Occurrence of Certain 'Caries-Inducing' Streptococci in Human Dental Plaque Material with Special Reference to the Frequency and Activity of Caries," *Archives of Oral Biology,* 13:911–918, 1968.

(8) Loesche, W. J., et al., "Association of *Streptococcus mutans* with Human Dental Decay," *Infection and Immunity,* 11:1252–1260, 1975.

(9) Loe, H., E. Theilade, and S. B. Jensen, "Experimental Gingivitis in Man," *Journal of Periodontology,* 36:177–187, 1965.

(10) Socransky, S. S., "Relationship of Bacteria to the Etiology of Periodontal Disease," *Journal of Dental Research, 49:203–222, 1970.*

(11) Jordan, H. V., P. H. Keyes, and S. Bellack, "Periodontal Lesions in Hamsters and Gnotobiotic Rats Infected with Actinomyces of Human Origin," *Journal of Periodontal Research, 7:21–28, 1972.*

(12) Kelstrup, J., and E. Theilade, "microbes and Periodontal Disease," *Journal of Clinical Periodontology, 1:15–35, 1974.*

(13) Peters, R. B., A. N. Bahn, and G. Barens, *"Candida albicans* in the Oral Cavity of Diabetics," *Journal of Dental Research,* 45:771–777, 1966.

(14) Killgore, G. E., et al., "Comparison of Three Anaerobic Systems for the Isolation of Anaerobic Bacteria from Clinical Specimens," *American Journal of Clinical Pathology, 59:552.559, 1973.*

(15) Mikx, F. H. M., et al., "Establishment of Defined Microbial Ecosystems in Germ-Free Rats: II. Di-association of Osborne-Mendel Rats with *Veillonella alcalescens* and Several Oral Microorganisms," *Caries Research,* 10:49–58, 1976.

(16) Loesche, W. J., "Periodontal Disease and the Treponemes," *in* "The Biology of Parasitic Spirochetes," edited by R. C. Johnson, Academic Press, New York, pp. 261–275, 1976.

(17) Slots, J., "The Predominant Cultivable Microflora of Advanced Periodontitis," *Scandinavian Journal of Dental Research, 85:114–121, 1977.*

(18) Kornman, K. S., and W. J. Loesche, "The Subgingival Microbial Flora During Pregnancy," *Journal of Periodontal Research, 15:111–122, 1980.*

(19) Shklair, I. L., and R. W. Renn, "The Distribution of *Pseudomonas Aeruginosa* in Human Saliva and Its Relationship to Gingival Health," *Journal of Periodontology,* 28:308–310, 1957.

(20) Loe, H., and C. R. Schiott, "The Effect of Mouthrinses and Topical Application of Chlorhexidine on the Development of Dental Plaque and Gingivitis in Man," *Journal of Periodontal Research,* 5:79–83, 1970.

(21) Nagle, P. J., and R. S. Turnbull, "Chlorhexidine: An Ideal Plaque Inhibiting Agent?," *Journal of the Canadian Dental Association,* 44:73–77, 1978.

(22) Flotra, L., et al., "A 4-Month Study on the Effect of Chlorhexidine Mouth Washes on 50 Soldiers," *Scandinavian Journal of Dental Research, 80:10–17, 1972.*

(23) Loesche, W. J., "Chemotherapy of Dental Plaque Infections," *Oral Science Reviews,* 9:65–107, 1976.

(24) Goldschmidt, P., R. Cogen, and S. Taubman, "Cytopathologic Effects of Chlorhexidine on Human Cells," *Journal of Periodontology,* 48:212–215, 1977.

(25) Gibbons, R. J., et al., "The Microbiota of the Gingival Crevice of Man: II. The Predominant Cultivable Organisms," *Archives of Oral Biology,* 8:281–289, 1963.

(26) Salkind, A., H. I. Oshrain, and I. D. Mandel, "Bacterial Aspects of Developing Supragingival and Subgingival Plaque," *Journal of Periodontology,* 42:706–708, 1971.

(27) Loesche, W. J., and S. A. Syed, "The Predominant Cultivable Flora of Carious Plaque and Carious Dentine," *Caries Research,* 7:201–216, 1973.

(28) Bowden, G. H., J. M. Hardie, and G. L. Slack, "Microbial Variations in Approximal Dental Plaque," *Caries Research,* 9:253–257, 1975.

(29) Jones, S., "Natural Plaque on Tooth Surfaces: A Scanning Electron Microscopy Study," *Apex,* 5:93–98, 1971.

(30) Newman, H. N., "Structure of Approximal Dental Plaque as Observed by Scanning Electron Microscopy," *Archives of Oral Biology,* 17:1445–1453, 1972.

(31) Listgarten, M. A., H. E. Mayo, and R. Tremblay, "Development of Dental Plaque on Epoxy Resin Crowns in Man: A Light and Electron Microscopic Study," *Journal of Periodontology,* 46:10–26, 1975.

(32) Guggenheim, B., "Ultrastructure and Some Biochemical Aspects of Dental Plaque: A Review," *in* "Microbial Aspects of Dental Caries," supplement to *Microbiology Abstracts—Bacteriology,* 1:89–107, 1976.

(33) Loesche, W. J., and S. A. Syed, "Bacteriology of Human Experimental Gingivitis: Effect of Plaque and Gingivitis Score," *Infection and Immunity,* 21:830–839, 1978.

(34) Holm-Pederson, P., N. Agerbaek, and E. Theilade, "Experimental Gingivitis in Young and Elderly Individuals," *Journal of Clinical Periodontology,* 2:14–24, 1975.

(35) Axelsson, P., and J. Lindhe, "The Effect of a Preventive Programme on Dental Plaque, Gingivitis and Caries in School Children: Results after One and Two Years," *Journal of Clinical Periodontology,* 1:126–132, 1974.

(36) Axelsson, P., and J. Lindhe, "Effect of Controlled Oral Hygiene Procedures on Caries and Periodontal Disease in Adults," *Journal of Clinical Periodontology, 5:133–151, 1978.*

(37) Nyman, S., J. Lindhe, and B. Rosling, "Periodontal Surgery in Plaque-Infected Dentitions," *Journal of Clinical Periodontology,* 4:240-249, 1977.

(38) Loe, H., F. von der Fehr, and C. R. Schiott, "Inhibition of Experimental Caries by Plaque Prevention: The Effect of Chlorhexidine Mouthrinses," *Scandinavian Journal of Dental Research,* 80:1–9, 1972.

(39) Bonesvoll, P., "Retention and Plaque-Inhibiting Effect in Man of Chlorhexidine after Multiple Mouth Rinses and Retention and Release of Chlorhexidine after Toothbrushing with a Chlorhexidene Gel," *Archives of Oral Biology,* 23:295–300, 1978.

(40) Bonesvoll, P., and P. Gjermo, "A Comparison between Chlorhexidine and Some Quaternary Ammonium Compounds with Regard to Retention, Salivary Concentration and Plaque-Inhibiting Effect in the Human Mouth after Mouth Rinses," *Archives of Oral Biology,* 23:289–294, 1978.

(41) Holbeche, J. D., and P. C. Reade, "In Vitro Studies on the Use of Cetylpyridinium Chloride as a Bacterial Plaque Control Agent," *Australian Dental Journal,* 23:328–331, 1978.

(42) Parsons, J. C., "Chemotherapy of Dental Plaque: A Review," *Journal of Periodontology,* 45:177–186, 1974.

(43) Spolsky, V. W., et al., "The Effect of an Antimicrobial Mouthwash on Dental Plaque and Gingivitis in Young Adults," *Journal of Periodontology,* 46:685–690, 1975.

(44) Carlson, H. C., K. Porter, and T. H. Alms, "The Effect of an Alexidine Mouthwash on Dental Plaque and Gingivitis," *Journal of Periodontology,* 48:216–218, 1977.

(45) De la Rosa, M., and O. P. Sturzenberger, "Clinical Reduction of Gingivitis Through the Use of a Mouthwash Containing Two Quaternary Ammonium Compounds," *Journal of Periodontology,* 47:535–537, 1976.

(46) Barnes, G. P., et al., "Effects of Two Cetylpyridinium Chloride-Containing Mouthwashes on Bacterial Plaque," *Journal of Periodontology,* 47:419–422, 1976.

(47) Ciancio, S. G., M. L. Mather, and H. L. Bunnell, "Clinical Evaluation of a Quaternary Ammonium-Containing Mouthrinse," *Journal of Periodontology,* 46:397-401, 1975.

(48) Gjermo, P., K. L. Baastad, and G. Rolla, "The Plaque-Inhibiting Capacity of 11 Antibacterial Compounds," *Journal of Periodontal Research,* 5:102–109, 1970.

(49) Compton, F. H., and G. S. Beagrie, "Inhibitory Effect of Benzethonium and Zinc Chloride Mouthrinses on Human Dental Plaque and Gingivitis," *Journal of Clinical Periodontology,* 2:33–43, 1975.

(50) Quigley, G. A., and J. W. Hein, "Comparative Cleansing Efficiency of Manual and Power Brushing," *Journal of the American Dental Association,* 65:26–29, 1962.

(51) Turesky, S., N. D. Gilmore, and I. Glickman, "Reduced Plaque Formation by the Chloromethyl Analogue of Vitamin C," *Journal of Periodontology,* 41:41–43, 1970.

(52) Silness, J., and H. Loe, "Periodontal Disease in Pregnancy: II. Correlation between Oral Hygiene and Periodontal Condition," *Acta Odontologica Scandinavica,* 22:121–135, 1964.

(53) Shick, R. A., and M. M. Ash, Jr., "Evaluation of the Vertical Method of Toothbrushing," *Journal of Periodontology,* 32:346–353, 1967.

(54) Elliott, J. R., and B. A. Clemmer, "On the Reproducibility of Periodontal Indices," *U. S. Navy Medicine,* 59:41–43, 1972.

(55) Loesche, W. J., "Clinical and Microbiological Aspects of Chemotherapeutic Agents Used According to the Specific Plaque Hypothesis," *Journal of Dental Research,* 58:2404–2412, 1979.

(56) Scherp, H. W., "Dental Caries: Prospects for Prevention," *Science,* 173:1199–1205, 1971.

(57) Loesche, W. J., "Topical Fluorides as an Antibacterial Agent," *Journal of Preventive Dentistry,* 4:21–26, 1977.

(58) Caldwell, R. C., et al., "The Effect of a Dextranase Mouthwash on Dental Plaque in Young Adults and Children," *Journal of the American Dental Association,* 82:124–131, 1971.

(59) Lobene, R. R., "A Clinical Study of the Effect of Dextranase on Human Dental Plaque," *Journal of the American Dental Association,* 82:132–135, 1971.

(60) Keyes, P. H., et al., "Dispersion of Dextranous Bacterial Plaques on Human Teeth with Dextranase," *Journal of the American Dental Association,* 82:136–141, 1971.

(61) Emilson, C. G., and J. Fornell, "Effect of Toothbrushing with Chorhexidine Gel on Salivary Microflora, Oral Hygiene, and Caries," *Scandinavian Journal of Dental Research,* 84:308–319, 1976.

(62) Johnson, R. H., and J. Rozanis, "A Review of Chemotherapeutic Plaque Control," *Oral Surgery, Oral Medicine, and Oral Pathology,* 47:136–139, 1979.

(63) Rogosa, M., J. A. Mitchell, and R. F. Wiseman, "A Selective Medium for the Isolation and Enumeration of Oral and Fecal Lactobacilli," *Journal of Bacteriology,* 62:132–133, 1951.

V. Astringents

A. General Discussion

1. *General comments.* An astringent is a substance capable of precipitating albumins and other proteins when applied topically to living cells of the mucous membranes and other tissues.

a. *Mode of action.* Astringents precipitate proteins. They form a thin protective film on the surface of the body cells. This film lessens their sensitivity to external stimuli, such as those of mechanical origin, those due to abrupt temperature changes, and those induced by chemicals. The action on an astringent is essentially limited to the cell surface. The permeability of the cell membrane is reduced, but the cells remain viable and uninjured unless high concentrations or excessive quantities are used, in which case the cell body is affected.

b. *Types and uses of astringents.* Various nontoxic metallic ions and certain organic acids can act as astringents. Derivatives of polyhydroxybenzoic acid, tannic acid, or similar protein-coagulating acids, will precipitate albumins and other proteins. Dilute aqueous solutions of aluminum and zinc salts are commonly used as astringents. Astringents have been alleged to promote healing of superficial lesions by acting as protective agents. Actually, there is no evidence that they promote the proliferation of epithelial or other type of cells and accelerate healing. Astringents merely provide symptomatic relief and are not curative.

Astringents are generally used in the mouth and throat to provide a protective coat over ulcerations, erosions, or abrasions of the mucosa, or over irritated or inflamed surfaces. Astringents are usually used in the form of dilute aqueous solutions. Concentrated solutions may be caustic and penetrate and precipitate the proteins in the interior of the cells, thus causing further injury, irritation, or ulceration. The protective coating often relieves various types of discomfort such as burning sensations, aches, or pains by diminishing or temporarily preventing access of offending stimuli to an irritated or injured surface. They do not possess analgesic activity nor do they depress receptors for pain as do anesthetics and analgesics.

c. *Adverse effects of astringents.* Since astringents are water soluble, they may be absorbed from the mucous membranes and produce systemic effects that are undesirable. Astringents containing tannic acid have caused adverse systemic effects such as liver injury, following absorption. The excessive and repeated use of solutions of metallic ions, e.g., iron and chromium, likewise, has resulted in absorption, causing adverse systemic effects. Use of concentrated solutions may cause irreversible injury to the cells; necrosis and sloughing occur. Some astringents possess varying degrees of antimicrobial activity due to their protein-coagulating properties. The protein-coagulating activity may be enhanced to an undesirable degree when certain antimicrobial agents are combined with astringents.

B. Categorization of Data

1. *Category I conditions under which astringents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.*

The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register**.

Category I Active Ingredients

Alum
Zinc chloride

a. *Alum.* The Panel concludes that alum is safe and effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Preparations of aluminum are widely used in medicine as antacids, antiseptics, and astringents. Aluminum solutions precipitate proteins in the same manner as do solutions of salts of many other metals. Dilute solutions of aluminum salts have an astringent action and are not irritating to the mucous membranes. More concentrated solutions act as irritants and may injure tissues. Insoluble preparations are used as antacids and adsorbents. The chief soluble preparation of aluminum used in medicine is alum or potassium aluminum sulfate ($KA1(SO_4)_2.10H_2O$). The insoluble aluminum hydroxides and phosphates are used as antacids. The acetate and chloride salts are water-soluble salts and are used as antiseptics and antiperspirants. They may also be used as astringents but are more irritating than the alums. Besides the potassium atom, the ammonium complex or sodium atom may be substituted for the potassium atom in the alum molecule. Thus, there are three types of alum-potassium, sodium, and ammonium—all with the same therapeutic effect, but with minor variations in solubilities and chemical properties. The potassium alum is the most commonly used derivative.

Potassium alum is also known as kalinite (Ref. 1). The technical product is also known as alum flour, alum meal, and cube alum. Alum is composed of colorless, odorless, hard, large transparent crystals. It has a sweetish astringent taste. Alum is stable at ordinary temperatures. It is generally available as the decahydrate, which becomes anhydrous above 200° C. One gram dissolves in 7.2 mL water, 0.3 mL boiling water, and is freely soluble in glycerol. Alum is insoluble in alcohol (Ref. 1). The aqueous solution is acidic (pH of 0.2 molar alum is 3.3). Anhydrous alum is sometimes called burnt or desiccated alum, and it attracts moisture from the air. The dodecahydrate is used for medicinal purposes.

(1) *Safety.* The Panel concludes that potassium alum is safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Small quantities of aluminum solutions induce no symptoms except a feeling of dryness and "astringency" (puckering) of the mucous membranes of the mouth and throat. Larger doses ingested orally pass into the stomach where they may act as gastric irritants and cause nausea and vomiting and, in extreme cases, exert a purgative effect (Ref. 2). Even when excessive quantities are ingested, no symptoms except those of gastrointestinal irritation and inflammation ensue. The continued use of alum does not result in any symptoms or result in chronic poisoning. Aluminum slats are absorbed only in small quantities from the stomach and intestine. Once they are absorbed, they are stored in the liver, kidney, muscles, and pancreas and slowly excreted into the bile and urine (Ref. 2).

Alum has been and is still used extensively in baking powders. It is estimated that in any ordinary diet seldom more than 60 mg aluminum is ingested per day. This quantity appears to be quite innocuous. Extremely large quantities of aluminum salts taken experimentally or with foods in the form of baking powders have produced diarrhea. No other adverse effects or symptoms of general poisoning have resulted from the ordinary use of such powders. The administration of large quantities of insoluble aluminum preparations to animals and man for use as antacids over long periods of time has produced no obvious symptoms of poisoning. Deaths from the ingestion of toxic doses are rare and attributable to the irritating action on the mucosa of the gastrointestinal tract.

Rats fed 2 mg alum daily did not show diminished growth or fertility or any other damage, even when these experiments were carried out for four generations (Ref. 2).

Practically no absorption occurs when insoluble aluminum-containing compounds are administered by mouth. The soluble salts and the insoluble derivatives that are solubilized by the acid in the stomach such as the hydroxide or the carbonate are absorbed, however. The entire amount of an insoluble aluminate is virtually recovered from the feces and only traces from the urine. When aluminum salt solutions are injected parenterally, they are excreted largely into the urine by the kidney. Some are excreted into the gastrointestinal tract. Organic derivatives of aluminum are used for human therapeutics, as for example, aluminum aspirin which is safe and effective.

(2) *Effectiveness.* The Panel concludes that alum is effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage section below.

The soluble salts of aluminum precipitate proteins. In view of this effect, they are astringent, styptic, and antiseptic in proper dosage. They are not corrosive to intact skin or mucous membranes of the mouth and throat. A 1-percent solution of aluminum acetate precipitates protein and most colloidal suspensions. This property is often employed for clarifying turbid water. The protein-precipitating properties are also used in the purification of toxins and antitoxins. The precipitated protein tends to redissolve in the presence of an excess protein. The precipitation of gelatin or serum proteins is maximal with 8 percent aluminum acetate. This concentration produces maximal contraction of excised rat tendon.

A 1-percent solution of aluminum acetate has been reported to be antiseptic, but the Panel does not regard this as an important therapeutic attribute of soluble aluminum salts. A 5-percent solution is germicidal. A saturated solution of potassium alum in 50 percent alcohol is employed for the prevention of bedsores (Ref. 3).

A 2-percent solution of potassium alum is used topically to suppress excessive sweating by hardening the skin. Aluminum chloride, which is more irritating than the other soluble salts since it is acidic in reaction, is sometimes used as a deodorant and to inhibit localized sweating of the feet and axilla (underarm) (Ref. 4). At first a 25-percent solution is applied twice a week and then later once a week.

Dilute solutions of potassium alum are effective astringents when applied to the mucous membranes of the oral cavity. They aid in the relief of sore throat or sore mouth or both by providing a protective coagulum over irritated or ulcerated surfaces. The relief is merely symtomatic and not due to any curative effect.

Alum is applied on the mucous membranes as an astringent in solutions of 0.5 to 1 percent. A 0.5- to 5-percent solution (Ref. 3) has been used for gargling, but is somewhat irritating and damaging to the teeth and is not recommended by the Panel.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 0.2- to 0.5-percent concentration of alum in aqueous solution in the form of a rinse, gargle, spray, or by swabbing the affected area, not more than three to four times daily. For children under 3

years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care astringent active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 49, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, PA, pp. 1282–1285, 1957.

(3) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, PA, pp. 48–49, 1973.

(4) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, NY, pp. 949–950, 1975.

b. *Zinc chloride.* The Panel concludes that zinc chloride is safe and effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Zinc chloride may be prepared by reacting metallic zinc with hydrochloric acid (Ref. 1). It may be molded into a pencil form. Since zinc is amphoteric, it is capable of forming acidic and basic compounds. If sodium hydroxide is added to a solution of zinc chloride, sodium zincate forms. In aqueous solution, the sodium zincate ionizes into a sodium cation and a ZnO_3 anion. Zinc chloride solution is acidic in reaction; the zincate is alkaline. Zinc salts are not compatible with alkalies and carbonates.

Zinc chloride, sometimes called "butter of zinc," is a white powder composed of deliquescent granules or fused pieces of rods. The solubility of zinc chloride in water is 432 g per 100 g at 25° C. It is soluble in 1.3 mL alcohol and 2 mL glycerol and is freely soluble in acetone. The aqueous solution is acidic on reaction (pH 4) (Ref. 1).

Solutions in water or in alcohol are generally slightly turbid, due to the presence of zinc oxychloride. Zinc chloride has been used as an astringent in mouthwashes in concentrations of approximately 1 percent. Pencils of zinc chloride and alcohol solutions containing up to 30 percent of the salt have been used for their caustic effects (Refs. 2, 3, and 4). Zinc chloride has been used in 0.5 percent concentrations as a vaginal douche for the treatment of *Trichomonas vaginalis* and also for the treatment of leukorrhea.

Numerous other preparations of zinc have been used for medicinal purposes. These may be divided into the soluble compounds such as the chloride, sulfate, or acetate, and insoluble compounds, such as the oxide, stearate, and carbonate, preparations. The insoluble preparations are used topically on the skin. Soluble preparations are used as astringents and for disinfection (Refs. 1 through 4).

(1) *Safety.* The Panel concludes that zinc chloride is safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Zinc is found in traces in foods and is indispensable in nutrition. Deficiencies of zinc ion in the diet may cause growth retardation, hypogonadism, skin changes, mental lethargy, and delayed wound healing. The major function of zinc in metabolism appears to be enzymatic. Zinc has been used as an antisickling agent in sickle cell disease. Zinc competes with cadmium, copper, lead, iron, and calcium for similar binding sites (Ref. 5). Various salts of zinc, such as the chloride, stearate, and sulfate, as well as the oxides, have been used externally and internally for the treatment of various dermatological conditions and inflammatory lesions of the mucous membranes of the mouth and throat (Refs. 3 and 4). Zinc sulfate has been used as an ophthalmic astringent solution at a concentration of 0.25 percent.

When taken internally, zinc salts irritate the gastric mucosa; for this reason zinc sulfate has sometimes been used internally as an emetic. It was once considered to be one of the most effective emetic agents for the treatment of poisoning, but it is not used in present day practices.

The intravenous lethal dose in rats in 60 to 90 mg/kg of zinc in a soluble salt. The lethal dose of zinc sulfate is estimated to be in the order of 15 g (Refs. 3 and 4). The oral toxicity of zinc compounds in man is low. Zinc compounds in quantities that might exceed the amount introduced in food, such as from zinc containers, appear to be innocuous. Zinc compounds caused no apparent symptoms or pathologic changes when administered daily for a year to dogs, cats, or rats. In some studies, no symptoms were noted when zinc compounds has been administered for a lifetime to several generations of animals. The zinc contents of the organs was not increased.

Systemic effects of intravenous injection of soluble zinc salts in man are mainly neurologic. Consciousness is lost without involvement of the motor areas. However, the subject is areflexic due to the comatose state. The blood pressure falls rapidly, probably as a result of the flocculation of plasma protein. Blood coagulation is retarded for approximately an hour after the injection of 5 to 50 mg/kg in rabbits, probably caused by a decrease in antithrombin. Long, continuous injection of zinc salts by catheter results in fibrotic changes in the acinar portion of the pancreas without affecting the islets. Chronic industrial zinc poisoning has been reported in workers in galvanizing plants. The symptoms in man are chiefly gastrointestinal (nausea and vomiting). Hypochromic anemia may also occur. Feeding zinc to rats produces hypochromic anemia and deficiency in growth (Ref. 4).

Inhalation of fumes of zinc oxide causes "metal fume fever." This is an industrial hazard noted among workers in plants where metallic zinc is heated. The zinc oxide is formed due to the oxidation of the metal. Inhalation of powdered zinc stearate produces the same symptoms. Presumably the crystals cause a temporary, reversible change in the epithelium of the respiratory tract.

Nasal sprays of zinc sulfate have been used to shrink the mucous membranes to allow drainage from infected accessory nasal sinuses. This type of treatment has the disadvantage in that it inhibits the activity of the cilia of the mucous membranes of the respiratory tract and favors the retention of secretions. Such decreased activity can also occur when these agents are applied to the mucous membranes of the oral cavity (Ref. 3).

(2) *Effectiveness.* The Panel concludes that zinc chloride is effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The salts of zinc are employed as astringents, corrosives, and mild antiseptics. They, most likely, owe their astringent effects to the ability of the zinc ion to precipitate protein. Soluble salts of zinc usually are almost completely ionized. Dilute solutions of zinc chloride and zinc sulfate are effective astringents. In high concentrations they are irritating to mucous membranes. The insoluble compounds, such as the oxide, or stearate, are used externally and are not irritating (calamine).

Dilute solutions of zinc chloride are effective astringents when applied to the mucous membranes of the mouth and

throat (Refs. 6 and 7). They aid in the relief of sore throat and sore mouth or both by providing a protective coagulum over irriated or ulcerated surfaces. The relief is merely symptomatic and not due to any curative effects.

The protein-precipitating properties of soluble zinc salts confer varying degrees of antimicrobial activity on these compounds, but the Panel does not recognize the use of these salts as antimicrobial agents because of the variability of their action and the fact that certain specific organisms are not affected by these agents. Zinc chloride, in concentration of 5 percent or more, has been used as an escharotic agent on granulations, ulcers, and similar lesions. The acetate and sulfate are less irritating than the chloride and are preferred when a mild astringent action is desired.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 0.1- to 0.25-percent concentration of zinc chloride in the form of a rinse or mouthwash or by swabbing the affected area with a cotton applicator, not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The panel recommends the Category I labeling for products containing oral health care astringent active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., editor, "Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 1307–1308, 1976.

(2) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gillman, Macmillan Publishing Co., New York, p. 1001, 1975.

(3) Sollmann, T., "A Manual of Pharmacology and Its Application to Therapeutics and Toxicology," 2d Ed., W. B. Saunders Co., Philadelphia, pp. 917–919, 1922.

(4) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1255, 1973.

(5) Prasad, A. S., "Clinical, Biochemical, and Pharmacological Role of Zinc," *Annual Review of Pharmacology and Toxicology,* 20:393–426, 1979.

(6) OTC Volume 130003.

(7) OTC Volume 130059.

Category I Labeling

a. *Indication.* "Aids in the temporary relief of occasional discomfort due to minor irritations of the mouth and throat."

b. *Warnings*—(1) *For all products containing oral health care astringent active ingredients.* (i) "Severe or persisent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which astringent active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC astringent oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredient

Tincture of myrrh

Tincture of myrrh. The Panel concludes that tincture of myrrh is not safe and not effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has classified tincture of myrrh as a Category II antimicrobial agent and has described its general characteristics elsewhere in this document. (See part IV. paragraph B.2.j. above—Tincture of myrrh.)

(1) *Safety.* The Panel concludes that tincture of myrrh is not safe as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has described the safety of tincture of myrrh elsewhere in this document. (See part IV. paragraph B.2.j. (1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that tincture of myrrh is not effective as an OTC astringent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel finds no controlled studies which substantiate claims that tincture of myrrh is an effective active ingredient with astringent activity (Ref. 1). Tincture of myrrh has been applied locally, allegedly to "stimulate spongy gums" and as a "protectant" for aphthous ulcers, sore mouth, and ulcerations of the throat (Refs. 2 and 3). Its effectiveness for this purpose is not substantiated with data from controlled studies. Tincture of myrrh has been employed in mouth rinses in the diluted form to treat stomatitis, but data on its effectiveness are not convincing. It has been used internally as a carminative (Ref. 3).

The Panel concludes that because tincture of myrrh is a mixture of many substances and no single ingredient has been identified in the mixture that is present in sufficient quantity to exert a therapeutic effect it has no place in modern therapeutics. Tincture of myrrh since has fallen into disuse in general medical practice and has been supplanted by other medicines whose therapeutic effectiveness as astringents has been established.

(3) *Evaluation.* The Panel concludes that tincture of myrrh is an oleoresin containing various substances which are irritating to the mucous membranes of the mouth and throat. Therefore it is not considered safe for topical application on these areas. The Panel also concludes that tincture of myrrh is a mixture of many substances, none of which appear to possess any astringent action.

References

(1) OTC Volume 130003.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 875–877, 1955.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 170, 1957.

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use, or for description of product attributes for products containing astringent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Temorpary relief of minor mouth and throat pain of aphthous ulcers."

(2) "Helps kill mouth germs."

(3) "Works directly on throat membranes."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Acts fast."

(2) "Quick relief of discomfort."

(3) "Has long-lasting beneficial effect."

(4) "Exerts a prolonged action."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Formula in use over ninety years."

(2) Adding such phrases as "plus," etc.

(3) "Superior new formulation."

(4) "A dentist's formula."

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "For pain after dental work."

(2) "Relief of uncomfortable conditions of the mouth and throat."

e. *Statements or phrases in the indications for use that state or imply that a product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "Relief of pain from aphthous ulcers (canker sores)."

(2) "Relieves stomatitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Helps prevent infection in burns, abrasions and minor cuts."

(2) "As an adjunct to oral prophylaxis."

(3) "Prophylaxis for Vincent's infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "As an adjunct to oral hygiene."

(2) "Helps remove mouth odors."

(3) "Helps the mouth feel clean."

(4) "For hygienic care of the mouth and throat."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or the type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Astringent."

(2) "Mouthwash."

(3) "Gargle."

(4) "Provides protective coating to mouth sores."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* None.

VI. Debriding Agents

A. General Discussion

1. *General comments.* Debriding agents are ingredients that soften, loosen, and remove exudates, mucus, and other secretions from the surface of irritated mucous membranes and lesions in the mouth and throat. Among these are peroxides, aqueous solutions of salts and detergents, hygroscopic agents, and enzymatic products. Debriding agents are exogenously applied to the mucous membranes to cleanse their surfaces. They differ from expectorants, which act endogenously by increasing the output of respiratory tract fluid.

a. *Mode of action.* Debriding agents act in a variety of ways. They may act mechanically, chemically, biochemically, physiochemically, or by any combination of these mechanisms. The peroxides are useful as debribing agents because they aid in the removal of debris from the mucosal surfaces by mechanical action. This results from the release of bubbles of oxygen by enzymatic activity when peroxides come into contact with the tissues. Solutions of electrolytes, such as sodium bicarbonate and saline, likewise act as debriding agents by mechanically washing the secretions from a surface. Mucus and certain secretions are softened or made fluid by alteration in pH. There is some evidence that increasing the alkalinity plays a role in reducing the tenacity and viscosity of mucus. Sodium bicarbonate is believed to act in this manner. Agents that soften or make the mucus less viscous are usually referred to as mucolytic agents. Detergents act as debriding agents by lowering surface tension. Certain enzymes may depolymerize mucopolysaccharides and render them less viscous.

Hypertonic sodium chloride solutions have been recommended for use as debriding agents since they act by osmosis and draw fluid out of tissues and cleanse mechanically. Hygroscopic agents, such as propylene glycol and glycerine, may also be applied topically to extract water from the tissues of the mouth and throat and thus reduce the viscosity of secretions and also act mechanically as cleansing agents.

Acetylcysteine allegedly reduces the viscosity of mucus in vitro by depolymerizing mucopolysaccharides. Detergents decrease surface tension and increase the wetting of tissues, thereby acting as cleansing agents. Supposedly they increase liquefaction of mucus.

b. *Use of debriding agents.* Debriding agents are used to aid in the symptomatic relief of sore mouth and sore throat. Thick, tenacious mucus, purulent secretions, and debris from desquamated cells may stimulate pain receptors in lesions such as ulcerations or inflamed areas of the mouth and throat. The removal of such secretions eliminates the stimulation and this relieves any ensuing discomfort. Debriding agents are not curative in any sense. They possess no direct, local anesthetic activity. They aid in relieving pain primarily by their protectant action. The effects of debriding agents are usually transient and of short duration, but the resultant relief of symptoms may outlast their duration of action. The peroxides, for example, may exert their debriding effects in a matter of minutes, but the relief of symptoms may last several hours.

c. *Absorption of debriding agents.* Most of the debriding agents described above are absorbed from the mucous membranes or from the gastrointestinal tract if swallowed. All those mentioned above are safe, since they are nontoxic unless used in excess or too frequently.

d. *Adverse reactions.* Adverse reactions may occur from the use of debriding agents, particularly from overuse. Overuse of the peroxides has caused sloughing of the mucous membranes. Inflammatory reactions may also occur from long-term use since some debriding agents may be locally irritating. Gastrointestinal disturbances may occur when some debriding agents are swallowed. The desiccating agents may cause dryness and enhance the severity of inflammatory lesions. Solutions that are excessively hypertonic may also act as desiccating agents and aggravate the symptoms. Sensitization may occur, but has not been reported following use of the debriding agents evaluated by the Panel.

B. Categorization of Data

1. *Category I conditions under which debriding agents for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

Carbamide peroxide in anhydrous glycerin (urea peroxide)
Hydrogen peroxide
Sodium bicarbonate

a. *Carbamide peroxide in anhydrous glycerin (urea peroxide).* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The general properties and safety of carbamide peroxide have been described above as an antimicrobial ingredient for use on the mucous membranes of the mouth and throat.

(See part IV. paragraph B.3.d. above—Carbamide peroxide in anhydrous glycerin (urea peroxide).)

(1) *Safety.* The Panel concludes that carbamide peroxide in anhydrous glycerin is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

It is the consensus of the Panel that the comments concerning the safety of carbamide peroxide as an antimicrobial agent are likewise applicable to its use as a debriding agent on the mucous membranes of the mouth and throat. (See part IV. paragraph B.3.d.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that carbamide peroxide is an effective OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Carbamide peroxide is dissolved in anhydrous glycerin or propylene glycol (Ref. 1). It is slowly decomposed into its components, urea and hydrogen peroxide, when it comes into contact with moisture, air, or light. When applied to living tissue, ulcerations of the mucous membrane, or mixed with saliva, blood, or other body tissue fluid or exudates containing the enzyme catalase, oxygen is released from the hydrogen peroxide in the form of fine bubbles. This causes frothing and foaming which aids in the dislodgement of dead, desquamated eipthelial cells, pus, or other organic material found in infected wounds and on ulcerations which effect their removal (Refs. 2 and 3). One part of carbamide peroxide releases five volumes of oxygen. The byproducts of the breakdown of carbamide peroxide are oxygen, water, and urea (Ref. 4). Tissues that contain peroxidases also cause the breakdown of hydrogen peroxide to oxygen, urea, and water, but the oxygen combines with a hydrogen acceptor and no free oxygen is released. Under these circumstances the ingredient would not be effective. The urea exerts no known therapeutic effect since urea is a normal constituent of body tissues resulting from the metabolism of protein. It exerts no known adverse effects on the mucous membranes since the quantity released in this reaction is not significant. In aqueous solutions the compound slowly decomposes, releasing oxygen, urea, and byproducts of its decomposition. This renders the preparation ineffective.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 10.0- to 15.0-percent concentration of carbamide peroxide in anhydrous glycerin undiluted by swabbing the affected area or use a 10.0- to 15.0-percent aqueous solution of carbamide peroxide in the form of a rinse, gargle, or spray, not more than three to four times daily. For children under 3 years of age, there is no dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.)

References

(1) Dale, J. K., and R. E. Booth, "Physical and Chemical Incompatibilities," *in* "Dispensing of Medication," 7th Ed., edited by E. W. Martin, Mack Publishing Co., Easton, PA, p. 284, 1971.

(2) OTC Volume 130016.

(3) OTC Volume 130017.

(4) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1266, 1976.

b. *Hydrogen peroxide.* The Panel concludes that hydrogen peroxide is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The general characteristics of hydrogen peroxide have been described elsewhere in this document. (See part IV. paragraph B.3.m. above—Hydrogen peroxide.)

(1) *Safety.* The Panel concludes that hydrogen peroxide is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Hydrogen peroxide is safe, when used as a 3-percent aqueous solution or when diluted with equal parts of water, for topical use on the mucous membranes of the mouth and throat.

The safety of hydrogen peroxide has been described elsewhere in this document. (See part IV. paragraph B.3.m.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that hydrogen peroxide is effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The effectiveness of hydrogen peroxide as an antimicrobial agent for use on the mucous membranes of the mouth and throat has been described elsewhere in this document. (See part IV. paragraph B.3.m.(2) above—Effectiveness.)

The usefulness of hydrogen peroxide as a debriding agent depends upon the release of nascent oxygen which presumably has a strong oxidizing effect and may chemically alter organic substances found in wounds and ulcerations of the mucous membranes and in pus.

When hydrogen peroxide comes into contact with tissues, it is converted to water and oxygen due to the action of the enzyme catalase. This reaction occurs very rapidly, and the bubbles of oxygen that are released effervesce, thereby loosening tissue, debris, mucus, pus, and other organic materials (Refs. 1, 2, and 3).

The release of oxygen occurs more rapidly in open wounds, on ulcerations, and on denuded areas of mucous membranes than it does on intact mucous membranes. It occurs in a healthy mouth since catalase is normally present in the saliva. Particles of food and debris present in the mouth and between the teeth may be dislodged. Little or no oxygen is released when hydrogen peroxide is applied to intact skin. The duration of action of hydrogen peroxide is brief because decomposition occurs very rapidly.

Removing organic debris by the mechanical action of oxygen release is probably the most important attribute of hydrogen peroxide. It is believed to be more so than its antimicrobial activity, since there is some doubt as to its effectiveness as an antimicrobial agent. This debriding action may aid in the relief of pain and discomfort due to sore throat and sore mouth. (See part IV. paragraph B.3.m.(2) above—Effectiveness.)

Hydrogen peroxide may be used full strength, but generally it is diluted with an equal volume of water. When used in closed cavities such as nasal sinuses for cleansing and irrigation, it is important that there be a vent for the escape of gas, otherwise pressure may be generated within a cavity of such magnitude to cause serious local injury. Furthermore, the unvented gas may even cause air emboli. The possibility that this may occur when hydrogen peroxide is used in the mouth or in the throat is remote, since all the spaces are free and open.

Prolonged topical use causes irritation of the buccal mucous membranes and, therefore, it should not be used more often than every 2 hours, for not more than 2 days.

(3) *Dosage.* Adults and children 3 years of age or older: Use a 3.0-percent concentration of hydrogen peroxide diluted with equal parts of water in the form of a rinse, mouthwash, gargle or spray, or apply with a swab, not more

than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part IV. paragraph B.1. below—Catetory I Labeling.)

References

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, p. 207, 1975.

(2) Darlington, R. C., "Topical Oral Antiseptics, Mouthwashes and Throat Remedies," *in* "Handbook of Non-Prescription Drugs," 4th Ed., edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, p. 131, 1973.

(3) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 545, 1968.

c. *Sodium bicarbonate.* The Panel concludes that sodium bicarbonate is safe and effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Sodium bicarbonate is also known as sodium hydrogen carbonate or sodium acid carbonate. Among consumers, it is known as baking soda. Its empirical formula is $NaHCO_3$ and it has a molecular weight of 84. The commercial preparation available in pharmacies and in groceries is 99.8 percent pure (Ref. 1).

Sodium bicaronate is a white crystalline powder or a powder consisting of granules. It begins to lose carbon dioxide at about 50° C (Ref. 1). At 100° C it is converted to sodium carbonate (NA_2CO_3), which is more alkaline. In a vacuum, sodium bicarbonate will release carbon dioxide. Sodium bicarbonate is readily decomposed into the salt of the acid and carbon dioxide by weak acids. In aqueous solutions, it begins to change into carbon dioxide and sodium carbonate at about 20° C and changes completely upon boiling. Sodium bicarbonate is soluble in 10 parts of water at 25° C and 12 parts of water at about 18° C. It is insoluble in alcohol (Ref. 1). Aqueous solutions of sodium bicarbonate prepared with cold water, without agitation, are slightly alkaline. Aqueous solutions slowly decompose on standing to carbon dioxide and sodium carbonate. The alkalinity increases due to this gradual conversion to sodium carbonate. The pH of solutions of sodium carbonate generally is between 8.0 and 8.2.

(1) *Safety.* The Panel concludes that sodium bicarbonate is safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

The fact that sodium bicarbonate has been used for such a long time in the preparation of various food products, in cooking, and medically in gastrointestinal disturbances attests to its safety. It has been used as an antacid for gastric hyperacidity, peptic ulcer, to alkalinize the urine in cases of urinary hyperacidity, and intravenously to correct the acid base balance in cases of acidosis, shock, etc. (Ref. 2).

When sodium bicarbonate is ingested, it interacts with the hydrochloric acid of the stomach. It is then converted to sodium chloride and carbon dioxide with the carbon dioxide often being released by belching. Externally, it has no irritating effect, and it has not been found to have any sensitizing effect on the mucous membranes (Ref. 3). The chief danger in the use of sodium bicarbonate lies in its overuse. This is particularly significant in the case of individuals with heart disease, hypertension, and renal disease, who must restrict their sodium ion intake. Sodium bicarbonate is not caustic to the skin or mucous membranes of the oral cavity. It is sometimes used as a paste for cleansing teeth and on the skin to relieve itching.

(2) *Effectiveness.* The Panel concludes that sodium bicarbonate is effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Sodium bicarbonate has been used parenterally to correct acidosis. It is also used externally as a cleansing agent in infections, for burns, scalds, urticaria, and various skin diseases. Sodium bicarbonate has been used as a cleansing douche in cases of vaginitis. The powder is orderless with a slightly saline and alkaline taste. The solution has a bitterish saline taste (Ref. 4).

Sodium bicarbonate soothes irritated skin and relieves the pain of minor acid burns. When used in a bath or as a dusting powder, it reduces the odor of sweat. Prompt application of moist sodium bicarbonate as a paste has helped relieve itching from nonpoisonous insect stings and bites (Ref. 4). Sodium bicarbonate, like other mild alkalies, combines with tissue proteins to form alkaline albuminates or with the cutaneous fats to form soaps. In this way it acts as an emollient and softens the epithelium of the skin.

Sodium bicarbonate has a mucolytic action due to its alkalinity. It favors the disintegration of mucus, separating the protein from the polysaccharide components of the mucoprotein chain. It has been used in inhalation therapy as an aerosol to liquidy the secretions of the tracheobronchial tree. When used as a spray, gargle, or rinse in the mouth and throat, it loosens and softens tenacious mucus so that expectoration is facilitated. This debriding action aids in the relief of pain and discomfort due to sore throat or sore mouth. Sodium bicarbonate possesses no antimicrobial activity, nor does it possess any analgesic properties. It is sometimes classed with expectorants, but it has no well defined expectorant activity. The debriding and mucolytic actions of aqueous solutions of sodium bicarbonate are primarily mechanical and chemical.

Sodium bicarbonate increases the alkalinity of the saliva of the mouth and throat, but this is temporary. Fresh saliva is constantly being secreted, and the sodium bicarbonate is washed away, restoring the original pH of the mouth.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 10.0-percent concentration of sodium bicarbonate combined with one-half teaspoonful of sodium chloride in a glass of warm water in the form of a gargle, not more than three to four times daily. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care debriding agent active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1109, 1976.

(2) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 1033–1034, 1977.

(3) OTC Volume 130025.

(4) Harvey, S.C., "Gastric Antacids and Digestants," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 966, 1975.

(5) Swinyard, E. A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., p. 736, 1975.

Category I Labeling

a. *Indication.* "Aids in the removal of phlegm, mucuc, or other secretions in

the temporary relief of discomfort due to occasional sore throat and sore mouth."

b. *Warnings*—(1) *For all oral health care products containing debriding agent active ingredients.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use for more than 2 days or administer to children under 3 years of age unless directed by physician."

(ii) "Discontinue use and consult a physician if irriation persists or increases, or if a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which debriding active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register**.

Category II Active Ingredients

Sodium perborate.

Sodium perborate. The Panel concludes that sodium perborate is not safe and not effective for use as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has classified boric acid and other derivatives containing elemental boron as Category II ingredients for use in the mouth and throat. The general characteristics of boron derivatives have been described elsewhere in this document. (See part IV. paragraph B.2.a. above—Boric acid.)

Sodium perborate is a white, crystalline powder, which is odorless, has a saline taste, and is stable in cool, dry air. It is decomposed with the evolution of oxygen in warm, moist air. In aqueous solutions sodium perborate decomposes into sodium metaborate and hydrogen peroxide. The solution gradually evolves oxygen. Heating accelerates the release of oxygen. One gram of sodium perborate dissolves in 40 mL of water (Ref. 1).

Sodium perborate is prepared by the interaction of boric acid or sodium borate with sodium or hydrogen peroxide. It is generally considered to be a derivative of pentavalent boron. Actually, sodium perborate is derived from the tribalent form and has a composition believed to be $NaBO_2 \cdot H_2 \cdot 3H_2O$. It contains less than 9 percent available oxygen by weight. Sodium perborate is decomposed by water to hydrogen peroxide and sodium metaborate (Ref. 2). Its decomposition is accelerated by enzymes found in the tissues in the mouth and in saliva such as catalase.

Sodium perborate is not considered safe because it is a derivative of boron, and when absorbed it is as toxic as boric acid and other boron derivatives. The Panel found no data concerning the acute or chronic toxicity of sodium perborate in animals or in man (Refs. 3, 4, and 5). Inasmuch as sodium perborate is unstable and decomposes on standing, to sodium metaborate and sodium borate, the Panel considers the data on the toxicity of boric acid to be applicable to sodium perborate. Continued use of sodium perborate causes hypertrophy of the papillae of the tongue and damage to the gums.

(1) *Safety.* The Panel concludes that sodium perborate is not safe as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

The Panel has described the safety of boric acid and boron toxicity elsewhere in this document. (See part IV. paragraph B.2.a.(1) above—Safety.)

(2) *Effectiveness.* The Panel concludes that sodium perborate is not effective as an OTC debriding agent active ingredient for topical use on the mucous membranes of the mouth and throat.

Sodium perborate has been used extensively in past years as an antiseptic for wounds (Ref. 6). Its antimicrobial activity is ascribed to its oxidizing effects resulting from the release of nascent oxygen (Ref. 7). A 2-percent solution was found to be as effective as an approximately 0.4-percent solution of hydrogen peroxide. It has also been used as a dusting powder combined with talc and other inert ingredients. Sodium perborate has been most frequently used for preparations of antiseptic mouthwashes for the treatment of acute necrotic ulcerogingivitis (Vincent's infection) (Ref. 7). The alkalinity of solutions of sodium perborate assists in the removal of mucus and food residues in the mouth and throat (Ref. 7). The instability of the solution requires that it be prepared at the time of usage. A saturated solution represents 2 percent of the salt. Ten to 20 percent is mixed with chalk for use as a dentifrice.

The alleged effectiveness of sodium perborate as a debriding active ingredient is believed to be due to the alkalinity of the solution and oxygen that is released when sodium perborate comes in contact with tissues, open wounds, and ulcerations.

(3) *Evaluation.* It is the consensus of the Panel that the quantity of oxygen released when sodium perborate is applied to tissues is insufficient to act mechanically as a debriding agent. Furthermore, sodium perborate is prepared from boric acid and is therefore a derivative containing elemental boron. It is not safe for use on the mucous membranes of the mouth and throat since it can undergo systemic absorption and be toxic. Sodium perborate is therefore placed in Category II from the standpoint of both safety and effectiveness.

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1118, 1976.

(2) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 843, 1957.

(3) OTC Volume 130048.

(4) OTC Volume 130071.

(5) OTC Volume 130093.

(6) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, p. 892, 1977.

(7) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 1072–1073, 1973.

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing debriding agent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Healing aid for minor oral inflammation."

(2) "Cleansing antiseptic for mouth and throat."

(3) "Antimicrobial cleansing agent."

(4) "Provides temporary pain relief."

(5) "Promotes flow of saliva."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Quickly removes phlegm and other secretions."

(2) "Fast acting."

(3) "Has long-lasting beneficial effects."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior cleansing agent."

(2) "Rapid acting with long lasting effects."

(3) Adding such phrases as "plus," etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "Forming, cleansing rinse for irritated throats."

(2) "Removes secretions causing sore throat caused by postnasal drip."

e. *Statements and phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, diagnosis of which must be made by a physician.* (1) "Helps against discomfort of canker sores."

(2) "Helps reduce inflammation."

(3) "For treatment of stomatitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* (1) "Removes disease causing germs by its cleansing action."

(2) "Prevents growth of odor forming bacteria."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "For mouth and gum care."

(2) "Soothing and cleansing to the mouth and throat."

(3) "A refreshing mouth rinse."

(4) "For oral hygiene."

(5) "Destroys odor forming germs."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic effect or class of a drug or the formulation containing the ingredient instead of designating the symptoms which the product is intended to relieve.* (1) "Debriding agent."

(2) "Mouthwash."

(3) "Gargle."

(4) "Cleansing agent."

(5) "Mouth rinse."

(6) "Cleansing antiseptic for the mouth and throat."

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* None.

VII. Decongestants

A. General Discussion

1. *General comments.* The vasomotor integrity of the mucosa of the naso- and oro-pharnyx and mouth depends upon the proper balance between sympathetic and parasympathetic efferent impulses. Activation of the parasympathetic division of the autonomic nervous system produces vasodilatation and increases secretions from the exocrine glands. Activation of the sympathetic division produces vasoconstriction and decreases glandular secretion.

Congestion of the mucosa of the upper respiratory tract is manifested by the engorgement of the blood vessels in the mucosa and passage of fluid from the capillaries into the tissue spaces. Congestion is usually caused by microbial infection, chemical irritation, allergy, and other such factors. Treatment is usually directed toward removing the cause. The symptoms may be relieved by eliciting sympathetic responses or blocking parasympathetic responses. Drugs that produce these responses and causes constriction of the blood vessels are called decongestants.

a. *Mode of action.* Stimulation of the parasympathetic nervous dilates the blood vessels and also activates the saliva and mucous glands causing an increase in secretions of saliva and mucus from the glands of the mucous membranes. Stimulation of the parasympathetic nervous system may aggravate the congestion. Activation of the sympathetic division usually does the reverse and relieves congestion. It may cause a thick mucous secretion to be released. Some alpha adrenergic drugs also possess a mild beta-stimulating vasodilating action. This is overshadowed by the alpha effect, but lingers on when the shorter alpha action has receded. Vasodilation may occur from this beta stimulation, causing a rebound effect and a return of symptoms of congestion.

Adrenergic agents are most commonly used for the symptomatic relief of nasal congestion. Adrenergic agents act by stimulating the alpha excitatory adrenergic receptors of the vascular smooth muscle, thus constricting the network of arterioles within the mucosa and reducing the flow of blood in the engorged edematous area. Opening of the obstructed nasal passages improves nasal ventilation and facilitates the aeration and drainage of the sinuses. Most decongestants are used topically, or ingested orally, or used in both ways. The response to topical application of nasal decongestants is prompt but variable in duration, whereas the response to oral therapy is slow and generally less intense and of longer duration. The nasal mucous membrane is more turgid than the oral and pharyngeal mucous membranes, and shrinkage is more obvious when decongestant drugs are applied to the nasal mucosa. The other mucous membranes, such as those of the mouth and throat, also respond to the action of vasoconstrictors.

b. *Uses of decongestants.* The Panel has considered the decongestant active ingredients and has deferred most of them to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products for evaluation since they are administered orally or parenterally and act systemically. Ordinarily labeling claims for topical use are made for their nasal effects. However, in evaluating certain products in the submissions, the Panel found that some decongestants were combined with other topically active ingredients in the form of lozenges. The labeling implied that the decongestant also acted locally on the mucous membranes of the throat and mouth. The Panel therefore felt obligated to evaluate the topical effects of these decongestants on the mucous membranes of the mouth and throat. The Panel noted that the quantities of decongestant ingredients incorporated in the product were less than the minimum recommended for a single dose for oral use by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. The Panel also noted that effectiveness of decongestants that are used topically in a "slow-release" dosage form, as would be the case when incorporated in a lozenge, was not considered by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In view of the fact that the topical application of these products stimulates adrenergic vasoconstriction locally, the Panel felt that these products should be evaluated from the standpoint of the local effect on the mucous membranes of the mouth and throat. No data were found to support the claim that decongestants are effective topically on the mucous membranes of the mouth and throat, or that the resulting vasoconstriction, should it occur, was of therapeutic benefit. On the other hand, there were no data available contradicting the fact that this occurs. The Panel, therefore, feels that in view of this lack of data, the decongestants mentioned in the products whose labeling indicates or implies that topical activity occurs in the mouth and throat, particularly the latter, should be considered with the oral health care products. In addition the Panel notes that vasoconstrictors combined with local anesthetics may prolong the analgesic effect by retarding the absorption of the drug.

c. *Adverse effects.* The topical application of decongestants sometimes

causes temporary discomfort, such as stinging, burning, or dryness of the mucosa. Various other adverse effects can be cited. One of the major disadvantages of the use of adrenergic blocking agents is the occurrence of rebound congestion after the vasoconstrictive action disappears. This is due to the fact that the beta stimulating effect of the drug lingers after alpha stimulation disappears. Some decongestants stimulate both beta and alpha receptors, and beta stimulation causes vasodilation. Recurrence or exacerbation of the original discomfort may cause the patient to apply or inhale the drug more frequently. Overdosage with signs of toxicity may result. Irritation from prolonged and continued use produces chronic swelling of the nasal mucosa. Whether or not this occurs in the oral mucosa has not been determined.

Topical decongestants also produce systemic reactions especially in infants and children or patients with cardiovascular diseases, hyperthyroidism, or patients taking monoamine oxidase inhibitors. Significant absorption can occur from the mucosa of the nasopharynx and the oropharynx, or from the gastrointestinal tract, when an excess of the solution trickles down the throat and is swallowed. Topical application of the decongestant may be the best way to avoid systemic absorption. Use of a spray held in the upright position minimizes accumulation since the medication and secretions drip from the nostril and are swallowed.

The systemic effects from overdosage of most adrenergic drugs include transient hypertension, tachycardia, nervousness, nausea, dizziness, palpitation, and occasionally central nervous system stimulation.

Adrenergic agents should be given sparingly and with caution to patients with hyperthyroidism, hypertension, diabetes mellitus, or ischemic heart disease.

B. Categorization of Data

1. *Category I conditions under which decongestant active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

None.

Category I Labeling

a. *Indication.* The Panel did not classify any decongestant active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel has proposed a Category III indication for decongestant active ingredients. (See part VII. paragraph B.3. below—Category III Labeling.)

b. *Warnings*—(1) *For all decongestant drug products.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

(3) *For products containing phenylephrine hydrochloride or phenylpropanolamine hydrochloride.*

(i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

2. *Category II conditions under which decongestant active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The panel recommends that the Category II conditions be eliminated from OTC decongestant oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

None.

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing decongestant active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statement or phrases which purport that a product exerts a pharmocologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Quiets rasping cough due to colds which may be causing discomfort."

(2) "For temporary relief of minor sore throat pain."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of ways by consumers, rather than in definite units of time.* (1) "Fast temporary relief of minor throat irritations."

(2) "Provides long lasting relief of mouth and throat discomfort."

(3) "Promotes healing."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Superior decongestant."

(2) "Multiaction formulation."

(3) Adding such terms as "plus," etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "Soothes tired throats."

(2) "Makes breathing easier."

(3) "Fights sore throat."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* (1) "Relieves sore throat pain due to postnasal drip."

(2) "Reduces inflammation."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom of disease state when proof that this occurs is lacking.* (1) "Helps prevent infection."

(2) "As an adjunct to prevent Vincent's infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Reduces mouth odors."

(2) "Makes mouth feel clean."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product is intended to relieve.* (1) "Decongestant for use on mucous membranes."

(2) "Oral spray."

(3) "Lozenge."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride

a. *Phenylephrine hydrochloride.* The Panel concludes that phenylephrine hydrochloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenylephrine hydrochloride as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine is the levo isomer of 3-hydroxyphenylethanol methylamine. In essence, it is epinephrine minus one hydroxyl group on the benzene ring at position number four (Ref. 1). The existing hydroxyl group is on position three. Phenylephrine is a synthetic, optically active sympathomimetic amine. It is a white, odorless, powder consisting of bitter-sweet crystals which are freely soluble in water or alcohol. Aqueous solutions of phenylephrine hydrochloride are either slightly acidic, or they are neutral to litmus. Phenylephrine hydrochloride melts between 140° to 145° C (Ref. 2). Phenylephrine acts at the alpha receptors. It is less potent than epinephrine, but is longer lasting.

(1) *Safety.* The Panel concludes that phenylephrine hydrochloride is safe as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine hydrochloride is safe and has a low degree of toxicity in man. The subcutaneous LD_{50} in mice is 1 g/kg. According to Gleason and associates (Ref. 3), the toxicity rating is 5. Phenylephrine hydrochloride is absorbed from the oral and gastric mucous membranes and produces a systemic sympathomimetic effect. Mild gastrointestinal symptoms are sometimes observed when large doses are administered by the oral route.

When the drug is administered intravenously, it produces an intense vasoconstriction and an elevation in diastolic and systolic pressure and a bradycardia (Ref. 4). The bradycardia is due to reflex vagal stimulation. Phenylephrine hydrochloride lacks a positive inotropic effect on the heart, which would increase the strength of that organ's muscular contraction. In large intravenous doses, it may produce intense vasoconstriction, a reflex bradycardia, and various types of arrhythmias. In cases of heart failure, it may cause pulmonary edema. With lesser intravenous dosages, ventricular extrasystoles and short paroxysms of ventricular tachycardia may occur. A sensation of fullness of the head and tingling of the extremities, likewise, is noted. Tremor, palpitation, and insomnia may occur in some patients. The pressor effect produced by sympathomimetic amines is markedly potentiated by monoamine oxidase inhibitors. Excessive elevation in blood pressure and hypertensive crises may occur when such drugs are used simultaneously (Ref. 1).

Parenteral or oral administration or topical use of phenylephrine hydrochloride may be contraindicated in patients with cardiovascular diseases, hypertension, severe arteriosclerosis or in patients with hyperthyroidism accompanied by tachycardia (Ref. 1). Phenylephrine hydrochloride solutions are contraindicated either topically or orally in persons with narrow-angled glaucoma. Overdosage of phenylephrine hydrochloride in susceptible individuals has resulted in a marked evaluation in blood pressure followed by cerebrovascular accidents. A reflex bradycardia results from the absorption of phenylephrine hydrochloride. This may be counteracted by atropine since it is due to reflex vagal stimulating effect. Phenylephrine hydrochloride should not be used simultaneously with monoamine oxidase inhibitors.

Solutions for topical use are sometimes preserved with agents such as sodium bisulfite, chlorobutanol, or methylparaben. These agents may cause local irritation or sensitization.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenylephrine hydrochloride as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylephrine hydrochloride is an effective alpha adrenergic drug that causes vasoconstriction and produces decongestion of mucous membranes when applied topically. Subsequently, parenteral phenylephrine hydrochloride produces an increase in arterial blood pressure and a reflex bradycardia without appreciably increasing the heart rate or cardiac output. Phenylephrine hydrochloride has little or no central stimulating action as does ephedrine and the amphetamine-type sympathomimetic drugs. Responses to phenylephrine hydrochloride are both locally and systemically more prolonged than with epinephrine.

Phenylephrine hydrochloride is used topically in a 0.25- to 1.0-percent solution as a nasal decongestant (Ref. 5). In some cases, it may produce marked local irritation. Phenylephrine hydrochloride acts by stimulating the alpha adrenergic receptors of the vascular smooth muscle of the mucous membranes of the nose, throat, and mouth, thus constricting the dialated network of arterioles and reducing the flow of blood (Refs. 6 and 7). This is most apparent in the nose since the mucous membranes are turgid in this area. Excessive use may produce congestion of the mucosa, and if sufficient quantities are absorbed, an elevation in blood pressure, dizziness, palpitations, and central nervous stimulation are sometimes observed. The secondary congestion of the mucous membranes is due to at least three factors, i.e., secondary vasodilation due to stimulation of beta adrenergic fibers by the phenylephrine hydrochloride effect which lingers beyond its alpha stimulatory action, increased capillary permeability due to vasoconstrictive ischemia, and local irritation. Phenylephrine hydrochloride has a low degree of irritancy and sensitizing potential.

Phenylephrine hydrochloride has been used in lozenges, with local anesthetics and other active ingredients to relieve sore throat (Ref. 8). There are no well-controlled studies demonstrating the effectiveness of phenylephrine hydrochloride as an effective decongestant on the mucous membranes of the mouth or throat nor is there sufficient evidence from controlled studies to indicate that decongestants provide symptomatic relief for irritation and pain or soreness of the mucous membranes of the mouth or throat. Phenylephrine retards the absorption of topically applied local anesthetics from the mucous membranes and prolongs their action.

The Panel notes that phenylephrine hydrochloride has been deferred to the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products for evaluation of its effectiveness systemically, when taken orally. The dosage recommended by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products as a Category I ingredient is 10 mg. The dose in the lozenge of the product submitted to the Oral Cavity Panel for evaluation is 5 mg (Ref. 8). The labeling for the

lozenge does not state if the ingredient acts systemically or topically. The implication is that it acts topically. The Oral Cavity Panel recommends that the mode of action be clarified in the labeling. If a topical action is meant, the labeling should so indicate. If the action is systemic the dose should conform to the recommended oral dose of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products, and the labeling should state that topical administration of this dose is effective systemically. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products has not so stated.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 5.0 mL of a 0.25-percent concentration of phenylephrine hydrochloride in normal saline in the form of a swab or spray, not more than three to four times daily. Use a lozenge containing 5 mg of phenylephrine hydrochloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.3. below—Category III Labeling.)

In addition, the Panel also recommends the following specific labeling:

Warnings. (i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care decongestants. (See part VII. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 908–909, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 948, 1976.

(3) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section II, p. 112, 1969.

(4) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 507, 1957.

(5) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 650–651, 1977.

(6) Innes, I. R., and M. Nickerson, "Drugs Acting on Postganglionic Adrenergic Nerve Endings and Structures Innervated by Them (Sympathomimetic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 506–510, 1970.

(7) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 326, 1965.

(8) OTC Volume 130058.

b. *Phenylpropanolamine hydrochloride.* The Panel concludes that phenylpropanolamine hydrochloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of phenylpropanolamine hydrochloride as an effective OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Phenylpropanolamine hydrocholoride is related structurally to the amphetamines (Refs. 1 and 2). It differs from ephedrine is having one less methyl radical and differs from the amphetamines in having a hydroxyl group on the aliphatic side chain. Thus, phenylpropanolamine hydrochloride is a sympathomimetic amine related both structurally and pharmacilogically to ephedrine and the amphetamines. It exerts most of its action on alpha adrenergic receptors.

Phenylpropanolamine hydrochloride is a white, crystalline powder with a slightly aromatic odor. It is decomposed by light. It is freely soluble in water and in alcohol, but insoluble in ether. Phenylpropanolamine hydrochloride melts between 190° and 194° C. Solutions of phenylpropanolamine hydrochloride are slightly acidic. Other names for phenylpropanolamine are norephedrine hydrochloride and propadrine hydrochloride (Refs. 1 and 3).

When applied locally phenylpropanolamine hydrochloride constricts capillaries and arterioles and shrinks the swollen mucous membranes of the mouth, the oropharynx, and particularly the nasal cavity. Systemically, it exerts a pressor effect and raises the blood pressure. Phenylpropanolamine hydrochloride has a longer duration of action and produces less central stimulation than ephedrine or the amphetamines (Ref. 1).

(1) *Safety.* The Panel concludes that phenylpropanolamine hydrochloride is safe as an OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

The toxicity rating by Gosselin and associates (Ref. 4) is 5. The lethal dose in man is approximately 50 mg/kg. The minimal lethal intraperitoneal dose in rats is 175 mg/kg. In mice acute toxicity is influenced by temperature. The LD_{50} is lower at 32° C than at 26° C (Ref. 5). The subcutaneous LD_{50} in mice is 850 mg/kg (Ref. 5). The minimal lethal dose in guinea pigs when administered subcutaneously is 600 mg/kg (Refs. 6 and 7). The intravenous LD_{50} in rabbits is 75 mg/kg, and the subcutaneous LD_{50} for the sulfate is 400 to 500 mg/kg (Ref. 6). In paired feeding experiments using oral doses of 2.4 mg/kg in rats for as long as 59 days, there was an initial decrease in food intake, but later, a return of the appetite. The rate of food passage through the gastrointestinal tract was decreased, but the digestion was not affected (Refs. 8 and 9).

Phenylpropanolamine hydrochloride is absorbed through the mucous membranes of the mouth and throat into the blood stream and causes a generalized sympathomimetic effect (Ref. 10). Large doses produce hypertension, headaches, tachycardia, restlessness, anxiety, sweating, tremor, extrasystoles, confusion, and delirium, whether taken orally or given parentally (Ref. 11). Administration of barbiturates partially relieves some of these symptoms. In general, untoward effects are minor in the majority of patients receiving therapeutic doses of the drug. Phenylpropanolamine hydrochloride causes a marked pressor effect if administered at the same time as monoamine oxidase inhibitors and is contraindicated for use in patients taking monoamine oxidase inhibitors (Ref. 12). It should be used with caution in patients with hypertension, cardiovascular diseases, hyperthyroidism, and diabetes (Ref. 13). It is contraindicated in patients with narrow-angle glaucoma and in patients with prostatic hypertrophy and in pregnancy.

Phenylpropanolamine hydrochloride has a low degree of irritancy and a low sensitizing potential. It interacts with

belladonna alkaloids and increases the incidence of side effects (Ref. 14). Phenylpropanolamine hydrochloride does not sensitize the heart to hydrocarbon anesthetics as do cyclopropane, chloroform, etc. (Ref. 15). Arrhythmias occur in nonanesthetized subjects due to its reflex vagal effects when the heart ejects blood against a constricted vascular bed, as is the case with other vasoconstrictors.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of phenylpropanolamine hydrochloride as a OTC decongestant active ingredient for topical use on the mucous membranes of the mouth and throat when used in the proposed dosage limit set forth below.

There are numerous studies, both controlled and uncontrolled, on the effects of phenylpropanolamine hydrochloride as an adrenergic agent (Ref. 12). Its action is primarily stimulation of alpha adrenergic receptors, since these are located in the arterioles and venules and not in the capillaries. Its vasoconstrictor effect is largely the result of its action upon the arterioles. Phenylpropanolamine hydrochloride acts on the mucous membranes of the mouth, nose, and throat when applied topically. It is most effective as a nasal decongestant, particularly in allergic rhinitis (Ref. 16). Phenylpropanolamine hydrochloride is also employed in bronchial asthma and as an antihypotensive agent during spinal anesthesia (Refs. 17 and 18). It is of little value as an anorexiant for control of obesity (Refs. 1 and 8).

Phenylpropanolamine hydrochloride is equally as effective, if not superior, to ephedrine as a sympathomimetic amine and as a vasoconstrictor (Ref. 2). Black (Ref. 19) compared phenylpropanolamine hydrochloride with ephedrine in 131 patients and found the symptomatic relief equal to that of ephedrine, but without the annoying side effects. Boyer (Ref. 20) used 0.75 g every 2 hours for 5 days or more and found phenylpropanolamine hydrochloride significantly more effective than other preparations. Solo (Ref. 21) found a marked vasoconstrictor effect lasting for periods up to 2 hours with a 3-percent aqueous solution in 300 patient studies. When the drug was applied topically, Murphy (Ref. 16) obtained good results with 0.75 g in adults and 0.375 g in children. Phenylpropanolamine hydrochloride is also used orally to produce systemic vasoconstriction, but is much more effective when applied topically in the nose. The vasoconstriction effect is more apparent in the nose than in the mouth and throat due to the turgidity that is characteristic of nasal mucosa compared to the oral mucosa. The duration of action of phenylpropanolamine adminstered topically is 2 to 3 hours and orally is approximately 4 hours.

There are insufficient data confirming the effectiveness of phenylpropanolamine hydrochloride as a decongestant on the mucous membranes of the mouth and throat. Furthermore, there are no studies that indicate phenylpropanolamine hydrochloride does not exert a beneficial effect in treating the symptoms, lesions, inflammations, or irritations in the oral cavity, since it is a topically acting vasoconstrictor.

Phenylpropanolamine hydrochloride has been used in the form of a lozenge with claims for relief of soreness of the mucous membranes of the mouth and throat. These lozenges contain, in addition to phenylpropanolamine hydrochloride, benzocaine and phenylephrine (Ref. 22). The quantity of phenylpropanolamine is less than the minimum effective orally administered dose recommended by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. Furthermore, that Panel has not considered the effectiveness of this ingredient systemically in subtherapeutic doses in a slow release dosage form as would be the case when incorporated in a lozenge for topical use. It is for these reasons that the Panel feels obligated to consider this ingredient in this combination. The quantity in the lozenge, if the drug acts systemically when absorbed after swallowing, is subtherapeutic.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 5.0 mL of a 0.25-percent concentration of phenylpropanolamine hydrochloride in aqueous solution in the form of a swab or spray, not more than three to four times daily. Use a lozenge containing 10.5 mg of phenylpropanolamine hydrochloride every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care decongestant active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care active ingredients. (See part IV. paragraph B.3. below—Category III Labeling.)

In addition, the Panel also recommends the following specific labeling:

Warnings. (i) "Do not use if taking monoamine oxidase inhibitors. Discontinue use if dizziness, headache, fast pulse, tremors, or nervousness develop. Consult a physician if symptoms persist."

(ii) "Do not use this product if you have thyroid disease, high blood pressure, diabetes, or heart disease except under the advice and supervision of a physician."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care decongestants. (See part VII. paragraph C. below—Data Required for Evaluation.)

References

(1) Osol, A., et al., "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., J. B. Lippincott Co., Philadelphia, pp. 898–899, 1960.

(2) Chen, K. K., C. Wu, and E. Henriksen, "Relationship between the Pharmacological Action and the Chemical Constitution and Configuration of the Optical Isomers of Ephedrine and Related Compounds," *Journal of Pharmacology and Experimental Therapeutics,* 36:363–400, 1929.

(3) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 950, 1976.

(4) Gosselin, R. E., et al., "Clincial Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 227, 1976.

(5) Warren, M. R., and H. W. Werner, "The Central Stimulant Action of Some Vasopressor Amines," *Journal of Pharmacy,* 85:119–121, 1945.

(6) Hartung, W. H., and J. C. Munch, "Amino Alcohols: I. Phenylpropanolamine and Para-tolypropanolamine," *Journal of the American Chemical Society,* 51:2262–2266, 1929.

(7) Hartung, W. H., "Epinephrine and Related Compounds: Influence of Structure on Physiological Activity," *Chemical Reviews,* 9:389–465, 1931.

(8) Tainter, M. L., "Actions of Benzedrine and Propadrine in the Control of Obesity," *Journal of Nutrition,* 27:89–105, 1944.

(9) Tonks, C. M., and A. T. Lloyd, "Hazards with Monoamine-oxidase Inhibitors," *British Medical Journal,* 1:589, 1965.

(10) Wantland, W. W., and D. Lauer, "Correlation of some Oral Hygiene Variables with Age, Sex, and Incidence of Oral Protozoa," *Journal of Dental Research,* 49:293–297, 1970.

(11) Humberstone, P. M., "Hypertension from Cold Remedies," *British Medical Journal,* 1:846, 1969.

(12) Mason, A. M. S., and R. M. Buckle, "'Cold' Cures and Monoamine-Oxidase

Inhibitors," *British Medical Journal,* 1:845–846, 1969.

(13) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispenstory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 910–911, 1973.

(14) Mitchell, C. A., "Possible Cardiovascular Effect of Phenylpropanolamine and Belladonna Alkaloids," *Current Therapeutic Research,* 10:47–53, 1968.

(15) Orth, O. S., et al., "Action of Sympathomimetic Amines in Cyclopropane, Ether and Chloroform Anesthesia," *Journal of Pharmacy,* 67:1–16, 1939.

(16) Murphy, J. A., "Propadrine Hydrochloride in the Treatment of Allergic Manifestations," *Pennsylvania Medical Journal,* 43:65–66, 1939.

(17) Lehmann, G., and L. O. Randall, "Pharmacological Properties of Sympathomimetic Diamines," *Journal of Pharmacology and Experimental Therapeutics,* 93:114–125, 1948.

(18) Loman, J., M. Rinkel, and A. Myerson, "Comparative Effects of Amphetamine Sulfate (Benzedrine Sulfate), Paredrine, and Propadrine on the Blood Pressure," *American Heart Journal,* 18:89–93, 1939.

(19) Black, J. H., "The Control of Allergic Manifestations," *The Journal-Lancet,* 57:101–102, 1937.

(20) Boyer, W. E., "The Clinical Use of Phenyl-propanol-amine Hydrochloride (Propadrine) in the Treatment of Allergic Conditions," *Journal of Allergy,* 9:509–513, 1938.

(21) Solo, D. H., "Phenylpropanolamine Hydrochloride as a Vasconstricting Agent in Otolaryngology," *Medical Record,* 153:101–102, 1941.

(22) OTC Volume 130036.

Category III Labeling

Proposed indication. "Aids in the temporaty relief of occasional discomfort due to congestion in the mouth and throat."

C. Data Required for Evaluation

The Panel agrees that the protocols recommended in this document for studies required to bring Category III drugs into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining such data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing topical decongestant drugs.* The effects of decongestant drugs should be determined by their ability to reduce edema, dilation of capillaries and other vessels, and other manifestations of congestion of the buccal and pharyngeal mucous membranes in patients with acute or chronic stomatitis, or pharyngitis and other areas involving the mucous membranes in the mouth and throat. The Panel recognizes that there are no established protocols for testing the effectivenss of this category of product. The Panel suggests that the outline below be utilized unless the investigators have at their disposal alternate methods acceptable to the FDA. Tests should involve double-blind placebo-controlled assessment of a drug's ability to relieve the congestion. Topically applied nasal decongestants stimulate the alpha adrenergic receptors of the vessels in the mucosa and cause vasoconstriction. The normal pink color disappears, and the mucous membrane apears pale. Edema is reduced.

The Panel suggests that direct observation of the affected area be made by three independent observers after topical application of a drug by swabbing, spraying, or other methods in the proposed dosage. Precautions must be taken to avoid swallowing, because that would result in both a systemic effect as well as a local effect. Subjective assessment by the patient of the effect of the drug on symptoms present is also desirable and should be recorded. The drug should be the same as that present in the OTC preparation. It should be applied in the same dosage or concentrations as indicated on the labeling and in the same manner as that recommended in the label concerning instructions for use of the preparation. Since topical decongestants may be administered repeatedly during episodes of congestion, studies should be conducted over the appropriate time intervals recommended for dosing to maintain optimal relief of symptoms. When testing locally applied decongestants in which rebound congestion may follow repeated use, the effect of the drug must be allowed to "wear off" and observations made to note if rebound occurs. When rebound is of concern, labeling should specify that the product is for short-term use and provides only temporary relief of congestion. Specific data should be obtained by testing the topical decongestant effect in the usual recommended concentrations and also at the maximum dosage frequencies recommended for periods of at least 1 week, in order to assess the incidence of severity of drug-induced rebound congestion and possibility of sensitization. Absorption of the decongestant may occur through the mucous membranes in sufficient quantities to produce a pressor effect. Blood pressure and pulse rate should be monitored during the testing.

2. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of stomatitis or pharyngitis with congestion. Patients should be grouped according to the similarity of the lesions and comparisons made between members of each group. The cross-over technique may be used for patients with chronic congestion, and they can serve as their own controls. Patients with acute infections may be studied, but the cross-over technique is not feasible because of the relatively brief course of acute disorders and the greater variation in the nature of the congestion that may be encountered. Larger numbers of these patients will have to be studied than with the cross-over group. They should be assigned in random fashion to placebo or drug groups. For comparative purposes, these groups must be matched by age, sex, and, if possible, the degree of congestion at the time of study. Smoking by test subjects should be prohibited 24 hours prior to and during the testing.

3. *Method of study.* Observations should include both subjective responses reported by the patient as well as objective data obtained by observing the congested area. If necessary and feasible, sequential colored photographs may be made for comparison before a placebo or drug is administered and at appropriate time intervals therafter to demonstrate onset, magnitude, and duration of the response. In testing the effect of decongestants upon the mucosa of the nasal passage, improvements in airflow and decrease in airway resistance are used as criteria of effectiveness of the drug in relieving congestion. The Panel suggests that such criteria may also be used for the mouth and throat in cases where the airway is compromised and the decongestant is responsible for an improvement.

4. *Interpretation of the data.* A recommended dose of the test drug should induce a statistically significant reduction in mucosal congestion when compared with a placebo response.

Evidence of drug effectiveness is required for a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to FDA must present both favorable and unfavorable results.

5. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing as outlined elsewhere in this document. (See part II. paragraph C.2.d. above—Safety evaluation.)

VIII. Demulcents

A. General Discussion

1. *General comments.* The following discussion of demulcents is based on a review of several sources (Refs. 1 through 4).

Demulcents are mucilaginous substances composed of gum, mucilages, starches, high molecular weight polyners of polyhydric alcohols and esters of polyhdric alcohols, polysaccharides, certain saccharides, and related colloidal materials. They form viscous solutions in water and a cohesive, protective film when applied to surfaces such as the skin or mucous membranes.

a. *Mode of action.* Demulcents are pharmacologically inert and nonreactive with tissue cell components. Their therapeutic usefulness is due to the fact that they protect the surface mechanically. They induce no changes in the cells with which they come in contact. When used for such purposes they are classed as active ingredients on the labeling. When applied to an inflamed, ulcerated, or otherwise sensitive cell surface, they retard movement or access of various chemicals, fluids, or air, and protect the surface from noxious stimuli produced by these agents. Some demulcents possess active adsorbing power and prevent noxious agents from sensitizing an irritated surface.

b. *Use of demulcents.* Demulcents may allay inflammation mucous membranes, especially those of the mouth and throat, by acting as protectants from chemicals and irritating stimuli. The effects are strictly local and due to physical rather than chemical action. Gums and other mucilaginous materials applied to a surface may exert a protective action against an irritant or poison. They may also be precipitant chemical antidotes for salts of heavy metals and other toxic substances. Demulcents are also used to emulsify oils, to suspend insoluble powders, and to delay the aborption of drugs. When used for this purpose, they are designated as pharmaceutical necessities and not as active ingredients. When used as pharmaceutical necessities, they are classed as inert ingredients on the labeling.

Mucilages and similar drugs derived from polysaccarides were formerly considered carbohydrate nutrients, but it has been shown that they are imperfectly digested and for the most part are absorbed and eliminated unchanged. Films of demulcents diminish the characteristic taste of many substances, such as acids, salts, and sweets as well as those that are bitter. They act by enveloping the substance and forming a protective layer over the mucous membrane. In this way they prevent access of the substance to the taste buds. In the case of acids, they act chiefly by adsorbing the acid on the surface of the colloidal particles. The acidic taste is minimized due to the decrease in concentration of the free form.

Demulcents interfere with the perception of various sensations such as cold, warmth, pressure, burning, or pain by protecting the receptors that mediate these sensations from agents that produce these stimuli. They exert no depressant effect on these receptors. They do not exert any anesthetic effect.

Among the numerous substances that have been used as demulcents are starch, gelatin, acacia, pectin, etc. When starch and gelatin are boiled with water, they undergo hydration and polymerization and become hydrophilic colloids. Gelatin forms a gel, and starch forms a paste. Acacia is a dry, gummy exudate derived from *Acacia senegal.* It forms a gummy viscous mass when dissolved in water, which acts as a demulcent on mucous membranes.

In essence, demulcents are protectants. Protectants are designed to cover the surface of a mucous membrane in order to prevent contact with irritants or noxious stimuli. Some protectants are powders that are in a very fine state of subdivision. They are used for dusting to form a coating over a lesion. Some demulcents form a semirigid fine coat when applied to a surface. Collodion, gelatin, methyl cellulose, and similar semiplastic material have been used on the skin and mucous membranes for this purpose. Attempts to use such substances on the mucous membranes have met with less success than on the skin.

Demulcents act as a barrier between the external environment and the surface of the mucous membranes. In addition they provide some mechanical support, which is a therapeutic advantage. They are more useful in this respect in preparations used on the skin rather than on the mucous membranes.

c. *Absorption of demulcents.* Most demulcents are inert and not absorbed. If absorbed, they are metabolized slowly or not at all. Demulcents are generally used in combination with other active ingredients. Some demulcents used on the mucous membranes of the mouth and throat form films for a short period of time because they are washed away by the saliva and swallowed and are therefore more useful than others that form persistent films. Demulcents applied to ulcerated surfaces or wounds on the mucous membranes of the mouth and throat fill depressions on these surfaces and thus remain in contact for a longer period of time than they do on the uninjured, healthy mucous membranes.

d. *Adverse reactions.* Demulcents do not cause serious adverse reactions because they are inert, nonirritating, and as a rule not haptenogenic. Demulcents obtained from biological sources that contain proteins and that may have not been purified can act as antigens.

References

(1) Grollman, A. R., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, pp. 191–193, 1947.

(2) Swingyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 946–947, 1975.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 130–131, 1957.

(4) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Testbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 606, 1965.

B. Categorization of Data

1. *Category I conditions under which demulcent active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

Elm bark
Gelatin
Glycerin
Pectin

a. *Elm bark.* The Panel concludes that elm bark is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Elm bark (slippery elm) is the dried inner bark of *Ulmus rubra* (Refs. 1 and 2). The tree itself is indigenous to the United States and Canada. In the spring the old bark is stripped from the trees, and some of the outer and all of the inner part is removed. It is this inner part that is used for therapeutic purposes (Ref. 3). The bark has a currylike odor. Elm bark contains mucilaginous substances which are readily extractable by water. Elm mucilage consists principally of a polysaccharide which on hydrolysis yields D-galactose, D-methyl galactose, L-rhamnose, and glucose. Elm also

contains traces of tannin, which exerts no significant pharmacologic or therapeutic effect. Elm bark also contains some starch and traces of oxalate salts. The total ash content is approximately 7 to 10 percent. A warm infusion prepared by boiling the bark in water was a folk remedy used in the treatment of cough and diarrhea. The bark was also used as a poultice to treat external inflammation (Refs. 1, 4, and 5).

(1) *Safety.* The Panel concludes that elm bark is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Little data were available in the literature or were provided in the submissions to the Panel concerning acute and chronic studies using elm bark in animals or in man (Ref. 6).

Elm bark is composed of polysaccharides that yield various innocuous sugars, and there have been no reports of adverse effects. It has enjoyed long-term use, and the Panel had judged elm bark to be a safe ingredient when used as a demulcent to treat symptoms of sore throat or sore mouth or both.

Elm bark was an official drug that was listed in the "United States Pharmacopeia" from 1820 to 1936 and in the "National Formulary" from 1963 until recently.

(2) *Effectiveness.* The Panel concludes that elm bark is an effective OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Ground elm bark yields a thick mucilage when digested in approximately 40 parts of cold water and incorporated into troches and lozenges. The mucilage rapidly forms a protective barrier over irritated and inflamed mucous membranes (Ref. 7).

There is no evidence that elm bark exerts any curative effects or promotes healing of lesions of the mucous membranes of the mouth and throat. Elm bark does not exert any anesthetic effect. Elm bark aids in the temporary relief of minor irritation or soreness of the mouth and throat (Ref. 6).

(3) *Dosage.* Adults and children 3 years of age and older: Use a 10.0- to 15.0-percent concentration of elm bark, incorporated in an agar or other water-soluble gum base, in the form of a lozenge every 2 hours if necessary. For children under 3 years of age, there is no recommended dosage except under the advice of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

(1) Stecher, P. G., editor, "The Merck Index," 7th Ed., Merck and Co., Rahway, NJ, p. 400, 1960.

(2) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 193, 1947.

(3) Youngken, H. W., "Drugs of Vegetable Origin," *in* "The Textbook of Pharmacognosy," 5th Ed., The Blakiston Co., Philadelphia, p. 272, 1943.

(4) Pratt, R., and H. W. Youngken, "Agents with a Physical Basis of Action," *in* "Pharmacognosy: The Study of Natural Drug Substances and Certain Allied Products," 2d Ed., J. B. Lippincott Co., Philadelphia, pp. 107–109, 1956.

(5) Trease, G. E., and W. C. Evans, "Pharmacognosy," 10th Ed., Williams and Wilkins, Baltimore, pp. 366–367, 1972.

(6) OTC Volume 130002.

(7) Wood, H. C., et al., "The Dispensatory of the United States of America," 23d Ed., J. B. Lippincott Co., Philadelphia, pp. 1186–1188, 1943.

b. *Gelatin.* The Panel concludes that geletin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin is a protein obtained by the partial hydrolysis of collagen derived from skinlike and other connective tissues and bones of animals. Gelatin may be derived from acid- or basic-treated precursors. When derived from an acid-treated precursor, the gelatin is known as Type A; when derived from a basic-treated precursor, it is known as Type B. Type A gelatin has an isoelectric point between PH 7.7 and 9.0; Type B has an isoelectric point between PH 4.7 and 5.0 (Ref. 1).

Gelatin is available in sheets, flakes, shreds, or as a coarse fine powder (Ref. 1). It is faintly yellow or amber with a slight bouillonlike odor and is almost insolube in cold water. When immersed in water it gradually swells, due to its hydrophilic properties, and softens to form a colloidal solution having varying degrees of viscosity. Thus, gelatin solutions are referred to as hydrophilic colloids. The viscosity of gelatin solutions decreases with increases of temperature. Dry gelatin can absorb 5 to 10 times its weight of water. It is readily soluble in hot water, but is insoluble in alcohol, chloroform, and ether.

Gelatin is used as a demulcent on the mucous membranes of the mouth, throat, and stomach. Gelatin also has many uses as a pharmaceutical nesessity such as in the preparation of jellies, suppositories, and for suspension of drugs and in the preparation of troches (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that gelatin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin is easily digested and used as a food as well as for medicines. Gelatin has been used as an adjuvant protein food, but is not a complete protein because it lacks certain essential amino acids, especially tryptophan. It cannot be used as a "complete" protein food unless it is combined with other proteins (Ref. 3).

The protective colloidal action of gelatin has been utilized in preparing modified milk formulas for infants. One to 2 percent gelatin lowers the curd tension of cow's milk. Gelatin solutions are amphoteric. This action makes them valuable as a food in cases of hyperacidic gastric states or in cases of peptic ulcer and other similar conditions because they can combine with acids by virtue of the amino groups on the amino acid molecules in the proteins.

The intravenous injection of gelatin solution greatly accelerates the ability of the blood to coagulate, and for this reason gelatin solutions were once used to treat internal hemorrhages (Ref. 3). Solutions of gelatin are difficult to sterilize, and unless the gelatin is absolutely pure, antigenic substances may be present and anaphylactic reactions may occur if administered intravenously. Gelatin is not a sensitizer when used topically and is devoid of any tendency to cause irritancy.

(2) *Effectiveness.* The Panel concludes that gelatin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Gelatin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in distant areas from stimulation by physical or chemical agents. There is no evidence that gelatin exerts any curative effect or promotes healing of lesions of the mouth or throat.

A special form of gelatin, known as absorbable gelatin sponge, may be used on mucous membranes. It is a sterile, absorbable, water-insoluble gelatin base sponge made by bubbling or agitating a solution of partially denatured gelatin with air and drying the foam in an oven.

Gelatin is carried away by the saliva and swallowed, making its effect only short-lived when applied to healthy

mucous membranes. Gelatin does not undergo digestion in the mouth since there are no proteolytic enzymes in the saliva.

Gelatin, by its protectant action, aids merely in the temporary relief of pain and discomfort due to sore throat and sore mouth. Gelatin is not an anesthetic. Any relief of discomfort it affords is due to its protectant effects.

(3) *Dosage.* Adults and children 3 years of age and older: Use a 5.0- to 10.0-percent concentration of gelatin in aqueous solution in the form of a rinse, gargle, spray, or by swabbing with an applicator or by applying digitally, as often as necessary. As lozenges or gels, use quantities sufficient to form a solid or semisolid state, as often as necessary. For children under 3 years of age there is no recommended dosage except under the advice of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 544, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 564, 1976.

(3) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 56–60, 1957.

c. *Glycerin.* The Panel concludes that glycerin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Glycerin is a trihydric alcohol. It is also known as 1,2,3-propanetriol, glycerol, and trihydroxy-propane (Ref. 1). Glycerin was discovered by Scheele in 1779 in fats from which glycerin may be released by hydrolysis. It is the alcohol that esterifies the oils and fats of plant and animal origin. Glycerin is a clear, colorless, viscous, hygroscopic liquid with a sweet taste and characteristic odor (Ref. 2). It is miscible with water and alcohol and insoluble in chloroform and fixed and volatile oils. Glycerin is markedly hygroscopic and takes up and retains water in its undiluted form. Next to water, it is probably the most widely used vehicle for medicinal substances for internal or external use. In addition to glycerin's solvent properties, its value as a vehicle depends on its viscosity, its water-absorbing property, its ability to lower the surface tension of water, its osmotic effect, and its ready miscibility with water and alcohol. The inclusion of glycerin in many medicinal preparations that contain water, retards the hydrolytic decomposition of some active ingredients. Solutions of medicinal substances in glycerin are called glycerites (Ref. 3). In addition, glycerin is valuable as a preservative in liquid dosage forms containing sugar because it is nonfermentable. Glycerin is said to have antimicrobial properties due to its dehydrating and desiccating effects. Its antiseptic action, however, is of no particular consequence as far as this Panel is concerned because it is not used for this purpose on the mucous membranes of the mouth and throat. It is ineffective unless it is present in sufficient concentrations to dehydrate bacteria (Ref. 4).

Glycerin is used to alter the viscosity and other physical properties of medicinal products. It acts as a sweetening agent and as a vehicle for drugs used in or about the mouth or in the throat. Glycerin is widely used in the preparation of rinses and mouthwashes, and it helps maintain the consistency of toothpastes (Ref. 5).

Anhydrous and concentrated glycerin causes irritation when applied to the mucous membranes because its hygroscopic property may cause desiccation of tissues. This osmotic effect is also partially responsible for the laxative action of glycerin suppositories (Ref. 6). When glycerin is used in dermatological preparations, it exerts an emollient effect. Glycerin is also classified as a pharmaceutical necessity (Ref. 2).

(1) *Safety.* The Panel concludes that glycerin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Long-term clinical use and extensive marketing experience have confirmed that glycerin is safe for internal use. Glycerin has been used over 100 years as a medicament. When injected intravenously glycerin causes crenation of the red blood cells due to its osmotic effect, and hemolysis and hemoglobinuria result. Toxicity after oral administration has not been reported.

Glycerin is innocuous when taken internally. It has been ingested by adults in 100-g doses for 50 days with no ill effects (Ref. 7). Diarrhea may occur following massive oral doses, due to its osmotic effects. Undiluted glycerin has been applied to the conjunctiva of rabbits, rats, and dogs with no grossly visible ill effects. Undiluted glycerin has also been applied to the buccal mucosa of rabbits, rats, and dogs without any visible adverse local effects. However, glycerin absorbs water and can be dehydrating and irritating to the mucous membranes, particularly if inflamed. When used undiluted it may absorb water from ulcerations and open wounds and produce pain, burning, or other manifestations of irritation. Aqueous solutions of glycerin are nonirritating and act as safe protectants to the mucous membranes and skin.

Glycerin is nonantigenic. Reports of systemic sensitization are virtually nonexistent. Irritation of the mucous membranes may occur from the hygroscopic properties when used undiluted. Local sensitization and local allergic reactions have not been reported and apparently do not occur.

(2) *Effectiveness.* The Panel concludes that glycerin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Glycerin acts as a demulcent when applied to the mucous membranes of the mouth and throat. It coats the mucous membranes with a thin adherent film. Glycerin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in diseased areas from stimulation by physical or chemical agents. There is no evidence that glycerin exerts any curative effect or promotes healing of lesions of the mouth or throat.

Concentrated glycerin absorbs water from tissues so that its soothing action is often preceded by smarting until it becomes diluted. It should, therefore, be diluted with two or three volumes of water or half a volume of 70 percent alcohol rather than used alone. This not only decreases its viscosity so that it is more easily applied, but also decreases its hygroscopic activity and desiccating effects (Ref. 8). Glycerin is absorbed from the mucous membranes. It is transported to the liver and transformed, to a certain degree, into glycogen and sugar.

Concentrations of 25 percent or more of glycerin manifest antimicrobial activity and are antiseptic due to its dehydrating effect. Undiluted glycerin destroys one tenth of the bacteria with which it comes in contact in 3 hours. It is not, however, useful as an antimicrobial agent. Glycerin allegedly increases the antimicrobial activity of phenol, thymol, and other antimicrobial agents (Ref. 8).

Glycerin, diluted with water, is indicated as a demulcent to aid in the temporary relief of minor irritations and

soreness of the mucous membranes of the mouth and throat. Glycerin manifests no anesthetic properties.

(3) *Dosage.* Adults and children 3 years of age and older: Use glycerin diluted with 2 or 3 volumes of water in the form of a rinse, mouthwash, spray, or by swabbing, as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent active ingredients. (See part VIII. paragraph B.1 below—Category I Labeling.)

In addition, the Panel recommends the following specific labeling: "*Warning.* Do not use full strength. Dilute with two or three volumes of water."

References

(1) Swinyard, E. A., and W. Lowenthal, "Pharmaceutical Necessities," *in* "Remington's Pharmaceutical Sciences," 15th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 1254–1255, 1975.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 581, 1976.

(3) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 196, 1947.

(4) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 116–117, 1965.

(5) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, pp. 245–246, 1977.

(6) "United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 223, 1975.

(7) Deichman, W., "Glycerol—Behavior in the Animal Organism (A Review of the Literature)," *Industrial Medicine,* 9:60–67, 1940.

(8) Sollmann, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 127–128, 1957.

d. *Pectin.* The Panel concludes that pectin is safe and effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

Pectin is a polysaccharide consisting chiefly or partially of polymerized methoxylated polygalacturonic acid molecules (Ref. 1). Pectin is obtained from the inner portion of the rind of citrus fruits, apples, and other botanical sources. The greater portion of pectin in fruit is present in a form known as propectin. Propectin is insoluble in water. This is converted into water soluble pectin by heating with a weak acid. The resulting product is purified by precipitating with alcohol or salting out with electrolytes.

Pectin is a mixture of polysaccharide molecules of various sizes. Pectin is not a single entity compound. Pectin is a coarse or fine yellowish-white powder (Ref. 2). It is soluble in 20 parts of water forming a viscous, opalescent, freely flowing colloidal solution. Pectin is insoluble in concentrated or diluted alcohol and other organic solvents.

The pectin molecules are large molecules of varying sizes. The molecular weights range between 150,000 and 300,000 daltons. It is composed of galacturonic acid anhydride molecules, some of which are partially methoxylated. Three carboxyl groups are present on each molecule of pectin. Some of these are esterified. The carboxyl groups impart acid properties to the molecule. Pectin forms gels which may be standardized to "150 jelly grade" by addition of dextrose or other sugars. Pectin may contain sodium citrate or other buffering agents. The viscosity and jelly strength of pectin depend primarily on the size of the molecules while the degree of methoxylation affects the setting time, reactivity with metallic ions, and other such characteristics. Certain nongalacturonide components, such as galactan and araban, may constitute one-third or more of pectin and may also modify its characteristics (Ref. 3).

(1) *Safety.* The Panel concludes that pectin is safe as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit ser forth below.

Pectin has been used in foods for jellies and medicinally as a demulcent and a pharmaceutical necessity. Pectin has been combined with kaolin and used as a protective agent for treating diarrhea (Ref. 4). An aquesous suspension consisting of 20 percent pectin and alpha kaolin is used as an intestinal adsorbent (Ref. 5). In the diet, pectin allegedly causes a lowering of serum cholesterol levels. The Panel does not consider this to be of any significane clinically if used occasionally, topically, and in limited quantities on the mucous membranes of the mouth and throat. Pectin solutions of an approximate 1-percent concentration were once used as plasma volume expanders in the treatment of hemorrhage and shock (Ref. 5). Pectin is no longer used for this purpose. It is retained and causes degenerative changes in the tissues.

Pectin has no adverse effects on the skin or mucous membranes. It is not irritating and nonantigenic. Sensitization has not been known to occur following topical application.

(2) *Effectiveness.* The Panel concludes that pectin is effective as an OTC demulcent active ingredient for topical use on the mucous membranes of the mouth and throat when used within the dosage limit set forth below.

When suspended in water, pectin forms a sol containing negatively charged, highly hydrated particles. Pectin is strongly hydrophilic.

Pectin is nearly neutral in reaction and is amphoteric, as are proteins. Pectin is more stable in acid than in alkaline media. In the presence of alkalies the methyl groups forming the esters are saponified and the glycosidic linkages that bind the glacturonic acid units may be disrupted and render the compound ineffective. Nongalacturonide components, such as galactan and araban, normally present in pectin may modify its characteristics when present in a proportion of one-third or more of the total weight of pectin.

Pectin exerts no pharmacologic effect of its own except that it acts as a demulcent and a protectant. It forms a cohesive film that holds a drug in contact with an irritated, inflamed, or ulcerated mucous membrane. Pectin does not retard would healing. Pectin provides a protective coating over irritated or ulcerated areas of the mouth and throat and prevents stimulation of receptors for cold, warmth, pressure, or pain by protecting these receptors in diseased areas from stimulation by physical or chemical agents. There is no evidence that pectin exerts any curative effect or promotes healing of lesions of the mouth or throat. Pectin exerts no anesthetic effect. Relief of discomfort is due to its protectant effects.

The term "150 jelly grade" indicates that pectin will produce a jelly when 1 part is mixed with 150 parts of sugar in a medium containing a final concentration of 55 percent sugar adjusted to the desired acidity. Less viscous preparations may be prepared for use in the oral cavity as a gargle, a rinse, or for direct application by swabbing.

(3) *Dosage.* Adults and children 3 years of age and older: Use a solution of pectin of desired viscosity in the form of a rinse, gargle, spray, or by swabbing, as often as necessary. Use quantities sufficient to form a solid or semisolid state in the form of lozenges or gels, as often as necessary. For children under 3 years of age there is no recommended dosage except uder the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral health care demulcent

active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

References

(1) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 845, 1973.

(2) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 915, 1976.

(3) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 611, 1965.

(4) Sollmann, T., "A Manual of Pharmacology and its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, p. 131, 1957.

(5) Swinyard, E. A., "Surface-Acting Drugs" *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 949, 1975.

(6) Grollman, A., and D. Slaughter, "Pharmacology and Therapeutics," 13th Ed., Lea and Febiger, Philadelphia, p. 820, 1947.

Category I Labeling

a. *Indication.* "Aids in the temporary relief of minor discomfort and protects irritated areas in the mouth and throat."

b. *Warnings*—(1) *For all oral health care products containing demulcents.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which demulcent active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral health care drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

None.

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing oral health care demulcent active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowing for OTC products.

a. *Statements or phrases which purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "For relief of sore throat due to smoking."

(2) "Helps reduce minor oral inflammation."

(3) "Promotes healing."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Given quick relief."

(2) "Acts fast."

(3) "Produces a smooth coating that gives quick comfort to irritated throats."

c. *Statement or phrases that allude to the superiority or greater potency of a product when compared to another product with a similar action.* (1) "Recommended by doctors."

(2) "Multiaction."

(3) "Superior new formulation."

(4) Adding such terms as "plus" etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* (1) "First aid to throat irritation."

(2) "Works directly on throat membrane."

(3) "Soothes tired throats."

(4) "Fights sore throat."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion the diagnosis of which must be made by a physician.*

(1) "To relieve discomfort due to stomatitis."

(2) "For relief of pain due to canker sores."

(3) "For relief of pain due to cold sores."

(4) "For relief of pain for minor sore throat due to common cold."

(5) "Relieves smokers sore throat."

(6) "Relieves pain due to tonsillitis."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a symptom or disease state when proof that this occurs is lacking.* "Prevents dryness of mouth and throat."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect.* (1) "Hygienic prevention."

(2) "Relieves dryness."

(3) "Reduces mouth odors."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symptoms which the product intended to relieve.* (1) "Demulcent."

(2) "Gargle."

(3) "Mouth rinse."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* None.

IX. Expectorants

A. General Discussion

1. *Introduction.* An expectorant is a substance that increases the output of respiratory tract fluid and promotes the expulsion of secretions from the lower and upper respiratory tract, mouth, or throat, thereby aiding in the relief of irritation or soreness of the mucous membranes of these structures. Expectorants are used to aid in the relief of symptoms due to inflammation or irritation in the lungs, bronchi, trachea, larynx, throat, and mouth. Expectorantia may actually be lifesaving when secretions are collecting in the larynx and trachea (in combination with other measures). Expectorants may indirectly facilitate the healing process by relieving these symptoms. There is no evidence that they have any direct action on the healing process.

a. *Mode of action.* Expectorants may act by one or a combination of the following mechanisms: (1) They may increase the volume of respiratory tract fluid. This results in a "thinning action" that facilitates removal of thick secretions resulting from a disease process in the mouth, throat, or respiratory tract. (2) They may promote the secretion of alkaline respiratory tract fluid in the bronchi, trachea, mouth, or throat. This reduces the viscosity of mucus and other secretions and debris in the mouth thereby facilitating their expulsion. They may reduce the viscosity of the secretions if volatilized and inhaled with steam and other propellants. This increases the secretory activity and increases expectoration. (3) They may act by promoting coughing, which mechanically dislodges the secretions in the lower respiratory tract and causes their expulsion. (4) They may stimulate the sensory endings of the vagus nerves, thereby causing an increase in watery secretion of the salivary glands and the mucous glands of the throat, esophagus,

stomach, and bronchi. This causes liquefaction and dissolution of thickened and viscous exudates and aids in the thinning of viscous mucus or purulent material in the upper air passengers or in the mouth and throat. (5) They may also increase salivation. By doing so they provide the antimicrobial activity of the saliva in addition to thinning secretions, etc.

Certain drugs, particularly those with cholinergic activity, promote the flow of saliva and are often referred to as sialogogues. Acids and small pieces of certain types of foods, such as pickles, may do likewise.

The secretions of the mucous membranes can be increased and made more fluid by various salts, such as ammonium chloride and potassium iodide. Potassium iodide increases output of various secretions, as is evident by the increase in lacrimal gland and nasal secretions in iodism. Secretions in the throat are also increased by potassium iodide.

Expectoration is actually a debriding process. There is, however, a distinct difference between expectorants and debriding agents. Expectorants Act endogenously and promote secretion of respiratory tract fluids. Debriding agents are substances that are added exogenously to mechanically assist in removal of debris from the mouth and throat.

b. *Uses of expectorants.* There is considerable doubt as to whether expectorants are of any therapeutic value. There is some evidence that expectorants may be effective in the lower respiratory tract. However, there is less evidence that expectorants are effective in the mouth and throat. Their effectiveness for relieving symptoms of sore throat or sore mouth has not been established with certainty. The term "expectorant" literally means "out of the chest," but it has been expanded to include some remedies that act in the throat. Some expectorants are excerted into the respiratory tract, throat, and mouth and act by local irritation. Expectorants acting by local irritation are termed "stimulant expectorants" because they stimulate the mucosa directly. Drug that promote expectorant activity by decreasing the viscosity of the mucus are called liquefying expectorants. Alkaline expectorants liquefy mucus by splitting the polysaccharide from mucoproteins. They may act above the larynx in the mouth and throat when used in a lozenge form. Most expectorants are swallowed.

c. *Adverse reactions.* Some expectorants in oral health care products may, if used to excess, be swallowded and cause gastric irritation. Iodides accumulate in the body and may cause iodism. Ammonium chloride may cause acidosis.

Expectorants may aggravate discomfort due to sore throat or sore mouth by inducing coughing if they increase the amount of lower respiratory tract fluid. Expectorants that cause local irritation may aggravate the symptoms of sore throat and sore mouth. Expectorants that are used systemically may be excreted in the saliva and cause a persistent, disagreeable taste which is unpleasant and may be irritating to lesions causing sore throat and sore mouth.

B. Categorization of Data

1. *Category I conditions under which expectorant active ingredients for topical use on the mucous membranes of the mouth and throat are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

None.

Category I Labeling

a. *Indications.* The Panel did not classify any expectorant active ingredient in Category I, but did place some ingredients in Category III. Because additional testing is necessary to determine the actual effect these ingredients have in the mouth and throat, the Panel did not place any indication in Category I. The Panel has proposed a Category III indication for expectorants. (See part IX. paragraph B.3. below—Category III Labeling.)

b. *Warnings*—(1) *For all oral health care products.*

(i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For oral health care products used in the form of gargles, mouthwashes, or mouth rinses.* "Try to avoid swallowing this product."

2. *Category II conditions under which expectorant active ingredients for topical use on the mucous membranes of the mouth and throat are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC oral cavity expectorant drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredient

Potassium iodide

Potassium iodide. The Panel concludes that potassium iodide is not safe and that there are insufficient data available to permit final classification of the effectiveness of potassium iodide as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium iodide is a colorless or white powder composed of cubical crystals or white granules. It is slightly deliquescent in moist air. Long exposure to light or moisture causes potassium iodide to become yellow due to liberation of iodine and small quantities of iodates. This can be prevented by the addition of small amounts of alkali. Aqueous solutions of potassium iodide are a colorless, odorless, neutral, or slightly alkaline (pH 7–9) liquid having a characteristically strong salty taste that can be masked by administering it in milk or various flavored syrups.

One gram of potassium iodide dissolves in 0.7 mL water, 0.5 mL boiling water, 22 mL alcohol, 8 mL boiling alcohol, 51 mL absolute alcohol, 8 mL menthol, 75 mL acetone, 2 mL glycerol, and about 2.5 mL glycol. Solutions of potassium iodide readily dissolve elemental iodine to form iodophors (Refs. 1 and 2).

Potassium iodide may be reduced to elemental iodide in the gastrointestinal tract. Both the elemental iodine and the salt are absorbed from all parts of the gastrointestinal tract. The kidney is the chief excretory organ for potassium iodide. Sixty-five to 80 percent of the iodide ion appears in the urine within 24 hours after the administration of a single dose of pottasium iodide. It is also found in tears, saliva, sebum, secretions from the nasal mucous membranes, sweat, feces, and milk (Refs. 3 and 4).

(1) *Safety.* The Panel concludes that potassium iodide is not safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat.

Potassium iodide, when used in doses considered to be therapeutically effective (300 mg every 4 to 6 hours) is not considered safe for use in OTC preparations. Although potassium iodide has been widely used in medical practice as an expectorant and for treating skin disorders and various other clinical conditions, adverse effects from its continued use are far from rare. The

action and toxic effects of potassium iodide are due to the iodide content.

Manifestations of toxicity due to iodides and iodine vary considerably not only in different individuals, but in the same individual at different times (Ref. 4). Side effects and toxic effects due to iodides are dose related. Iodism develops in practically all persons chronically treated with high doses of iodide compounds. However, some individuals are highly sensitive to iodides and react to the first few doses with serious symptoms (Ref. 5). Anaphylaxis and other allergic manifestations have been reported.

The commonest symptom of iodism is inflammation of the mucous membranes (catarrh) of the respiratory passages, especially the nose. Occasionally swelling, edema, and small ulcers in the larynx develop. Severe respiratory obstruction necessitating tracheotomy has been reported. Bronchitis has also been reported in humans following the use of potassium iodide. Profuse watery secretions often resulted in these cases. In animals, edema of the lungs and pleuritic effusions have followed the injection of iodides. Other symptoms of iodism include salivation, coryza, sneezing, conjunctivitis, headache, fever, laryngitis, stomatitis, parotitis (iodine mumps), various skin rashes (iododerma, thrombotic thrombocytopenic purpura), brassy taste, burning of the mouth and throat, chronic sore gums and teeth, and symptoms of a head cold may also result. Edema of the glottis, necessitating tracheotomy, has also been reported following the use of potassium iodide (Refs. 4 and 6).

Carswell, Kerr, and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death, apparently resulting from congenital goiter caused by iodides compressing the trachea, were reported by Galina, Avnet, and Einhorn (Ref. 8). Continued excessive use of iodide in children and adults may produce goiter or hypothyroidism or both (Refs. 9 and 10). The "Medical Letter on Drugs and Therapeutics" (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as a frequent cause.

Iodides generally induce nausea and gastric discomfort. A single dose of potassium iodide increases the volume of gastric juice secreted and prolongs the elaboration of secretions aroused by the taste of food. Large quantities of iodides also cause irritation of the stomach due to a local salt action on the mucosa. Nausea, vomiting, and, more rarely, diarrhea result. These adverse reactions may occur with single doses and necessarily a manifestation of iodism.

Other adverse reactions have been reported by Shelly (Ref. 12). He discussed the systemic manifestations of two patients who had iodism. These included hepatitis, fever, leukocytosis, hypoproteinemia, hypocalcemia, and an elevation of serum transaminase and alkaline phosphatase. A challenge with 500 mg of orally administered potassium iodide reproduced a typical attack.

Skin eruptions occur frequently in iodism particularly after prolonged treatment. These eruptions may simulate almost all known skin diseases; however, the most common manifestations are erythematous patches, or papular eruptions. These may progress into pustules or into larger inflamed areas (Ref. 4).

Falliers et al. (Ref. 13) reportedly found a high incidence of adverse reactions in a double-blind crossover study of 52 asthmatic children on iodide therapy. One child developed a papulovesicular eruption, and treatment was discontinued. Sixteen adolescents developed acneiform lesions. Eighteen patients developed thyroid enlargement but no evidence of suppressed thyroid function. Leonardy (Ref. 14), in discussing the use of iodides in the treatment of bronchial asthma, cited a review by Peacock and Davison (Ref. 15) involvig 500 patients. In this series, 13.5 percent of the patients developed reactions of such severity that treatment was discontinued.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit the final classification of the effectiveness of potassium iodide as an OTC expectorant for topical use on the mucous membranes of the mouth and throat.

Although there is experimental evidence that indicates that potassium iodide increases the secretion of respiratory tract fluid (RTF), such evidence is from uncontrolled studies and is sparse and unconvincing. Thus, the therapeutic efficacy of potassium iodide is doubtful (Ref. 16). The presence of iodides in the RTF has been demonstrated in animals, but whether this increases the amount of RTF secreted or morely decreases its viscosity is not established (Refs. 17 and 18).

Potassium iodide is believed to increase bronchial secretions in the respiratory tract by reflex stimulation of the gastric mucosa. It is believed to act in the same manner as ammonium chloride. There are no data substantiating that this reflex stimulation causes an increase in the secretions from the glands of the mouth and throat. The use of the drug is limited by its unpleasant taste and frequency of adverse reactions.

Potassium iodide has been used as a gargle, in lozenges, troches, and "cough drops" presumably to stimulate the flow of saliva and to prevent the "drying out" of the pharyngeal mucosa.

Falliers et al. (Ref. 13), in a 3-year, double-blind study in 52 children with chronic asthma, using 300 mg, three times daily, demonstrated a statistically significant improvement in symptoms. Those receiving iodides improved, but there was a wide variation in the response. This study, however, does not lend any support to the effectiveness of potassium iodide used topically on the mucous membranes of the mouth and throat.

(3) *Evaluation.* The Panel concludes that potassium iodide is not safe and that there are insufficient data on its effectiveness as an OTC expectorant active ingredient for topical use in the mouth and throat.

References

(1) Modell, W., editor, "1964–1965 Drugs of Choice," The C. V. Mosby Co., St. Louis, pp. 504–505, 1964.

(2) Stecher, P. G., editor, "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 855, 1968.

(3) Peach, M. J., "Anions: Phosphate, Iodide, Fluoride, and Other Anions," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 800–803, 1975.

(4) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, pp. 1015–1020, 1965.

(5) Harden, R. M., "Submandibular Adenitis Due to Iodide Administration," *British Medical Journal,* 1:160–161, 1968.

(6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 78, 1976.

(7) Carswell, F., M. M. Kerr, and J. H. Hutchison, "Congenital Goitre and Hypothroidism Produced by Maternal Ingestion of Iodides," *The Lancet,* 1:1241–1243, 1970.

(8) Galina, M. P., N. L. Avnet, and A. Einhorn, "Iodides During Pregnancy: An Apparent Cause of Neonatal Death," *The New England Journal of Medicine,* 267:1124–1127, 1962.

(9) Chapman, R. S., and R. A. Main, "Diffuse Thinning of Hair in Iodide-Induced Hypothyroidism," *British Journal of Dermatology,* 79:103–105, 1967.

(10) Begg, T. B., and R. Hall, "Iodide Goitre and Hypothyroidism," *Quarterly Journal of Medicine,* 32:351–362, 1963.

(11) Aaron, H., et al., "Drug-Induced Goiters in the Fetus and in Children and Adults," *The Medical Letter on Drugs and Therapeutics,* 12:61–62, 1970.

(12) Shelley, W. B., "Generalized Pustular Psoriasis Induced by Potassium Iodide," *Journal of the American Medical Association,* 201:1009–1014, 1967.

(13) Falliers, C. J., et al., "Controlled Study of Iodotherapy for Childhood Asthma," *Journal of Allergy,* 38:183–192, 1966.

(14) Leonardy, J. G., "The Use of Iodides in Bronchial Asthma," *Southern Medical Journal,* 61:959–962, 1968.

(15) Peacock, L. B., and H. M. Davison, "Observations on Iodide Sensitivity," *Annals of Allergy,* 15:158–164, 1957.

(16) "AMA Drug Evaluations," 3d Ed., Publishing Science Group, Littleton, MA, pp. 655 and 659, 1977.

(17) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," *Pharmacological Reviews,* 6:521–542, 1954.

(18) Boyd, E. M., et al., "The Effect of Inorganic and Organic Iodides Upon the Output of Respiratory Tract Fluid," *Canadian Journal of Research, 23:195–205, 1945.*

Category II Labeling

The Panel concludes that the following statements or phrases are not acceptable in the labeling as indications for use or for description of product attributes for products containing expectorant active ingredients. They are not supported by scientific data or sound theoretical reasoning or are inaccurate or make claims that exceed those allowed for OTC products.

a. *Statements or phrases that purport that a product exerts a pharmacologic or therapeutic action which it does not possess or is not an attribute of the product or which is in doubt or cannot be proven to occur.* (1) "Temporary relief of sore throat due to the common cold."

(2) "Relieves stuffed up feeling."

(3) "Subdues cough reflex."

(4) "Relieves mouth and throat pain."

(5) "Works internally to break up phlegm."

b. *Statements or phrases which indicate the time of onset or duration of action of a product in general, nonspecific terms that can be interpreted in a number of different ways by consumers, rather than in definite units of time.* (1) "Provides prompt relief of throat discomfort."

(2) "Rapidly relieves discomfort."

(3) "Fast relief."

c. *Statements or phrases that allude to the superiority or greater potency of a product when compared to another product with similar action.* (1) "Superior expectorant."

(2) "Improved formulation."

(3) Adding terms such as "plus" etc.

d. *Statements or phrases that are vague in their meaning and cannot be readily understood or are misleading.* "Provides relief by local cleansing action."

e. *Statements or phrases in the indications for use that state or imply that the product is to be used to treat a disease process or lesion, the diagnosis of which must be made by a physician.* "Healing aid for minor oral inflammations."

f. *Statements or phrases that indicate that a product acts prophylactically and prevents development of a disease state or symptom when proof that this occurs is lacking.* (1) "Soothing and cleansing to the mouth and throat."

(2) "Prevents infection."

g. *Statements or phrases that indicate that a product is used for cosmetic purposes, but imply that a product exerts a therapeutic effect.* (1) "For mouth and gum care."

(2) "Promotes oral hygiene."

h. *Statements, phrases, or terms in the indications for use that describe the pharmacologic or therapeutic action or class of a drug or type of formulation containing the ingredients instead of designating the symtoms which the product is intended to relieve.* (1) "Expectorant."

(2) "Promotes salivation."

(3) "Mouthwash."

(4) "Promotes needed expectoration."

3. *Catefory III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

Ammonium chloride
Horehound
Tolu balsam

a. *Ammonium chloride.* The Panel concludes that ammonium chloride is safe, but that there are insufficient data available to permit final classification of the effectiveness of ammonium chloride as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Ammonium chloride is also known as muriate of ammonia and sal ammoniac. It occurs as colorless crystals, or a white, fine, or coarse crystalline powder. One gram of ammonium chloride is soluble in about 3 mL water, about 100 mL alcohol, about 8 mL glycerin, and about 1.4 mL boiling water (Ref. 1). Ammonium chloride has been used for many years as a medicinal agent.

(1) *Safety.* The Panel concludes that ammonium chloride is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Clinical experience over many years of use has confirmed that the oral administration of ammonium chloride is safe when used in the dosage range recommended as an expectorant. The LD_{50} in rats of ammonium chloride given intramuscularly is 30 mg/kg. There are no controlled clinical studies documenting the safety of the drug when used topically on the mucous membranes of the mouth and throat; however, its long-term clinical use attests to its safety.

There are numerous human studies documenting the occurrence of progressive hyperchloremic acidosis when ammonium chloride is used orally, especially in patients with renal, hepatic, or pulmonary insufficiency (Refs. 2 through 5). Most of these occurred with doses in excess of 6 to 8 g per day. The drug was formerly used as a diuretic for the treatment of heart failure. Relmane, Shelburne, and Talman (Ref. 6) reported two nearly fatal cases following the ingestion of excessive amounts (82 g in a 48-hour period). Ticktin, Fazekas, and Evans (Ref. 7) have described a case of hepatic coma precipitated by an 8-g dose of ammonium chloride in a patient with congestive heart failure. When the oral dosage range of 250 to 500 mg 4 to 6 times daily has been used, the customary dose for use as an expectorant, the most common adverse reactions have been nausea and in some cases vomiting (Ref. 8).

Ammonium chloride is rapidly absorbed from the gastrointestinal tract following oral administration. Complete absorption occurs within 3 to 6 hours. Oral administration of relatively large doses of ammonium chloride may induce nausea and vomiting (Ref. 9). In patients with renal insufficiency a progressive hyperchloremic acidosis occurs. In the presence of liver disease, it may cause ammonia intoxication similar to that occurring spontaneously in hepatic coma (Refs. 5 and 10).

After oral administration, some ammonium chloride is excreted unchanged into the urine, while some is converted to urea. Transformation to urea occurs in the liver and proceeds rapidly. The end products are urea and hydrochloric acid. The latter reduces the alkaline reserve in the blood, producing acidosis.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of ammonium chloride as an OTC expectorant active ingredient

for topical use on the mucous membranes of the mouth and throat.

The ammonium ion is believed to exert an expectorant action, and its salts are extensively used for this purpose (Refs. 11), but the evidence to support this contention is not convincing. However, the ammonium salts are rarely used alone but are used in combination with other ingredients (Ref. 5). The chloride is the salt most commonly prescribed for its effect on the respiratory mucous membranes and is a common constitutent of many expectorant mixtures (Ref. 12). The lozenge is often used for treating symptoms of sore throat. The salt is believed to exert its expectorant action by reflexly stimulating the vagal nerve endings in the mucosa of the stomach. Irritation of the gastric mucosa has been shown experimentally to cause an increase in secretion of respiratory tract fluid in the mouth, throat, larynx, trachea, and bronchi (Refs. 5, 10, 13, and 14). Of all the ammonium salts, the chloride appears to be the most effective for decreasing the viscosity and diminishing the tenacity of mucus. Following the administration of ammonium chloride, traces of ammonium carbonate are formed in the bronchial mucous membrane. This is alkaline and aids in liquefying the mucus; it also stimulates the ciliary movements which facilitate expectoration of mucus and debris resulting from a disease process (Ref. 15).

Goth (Ref. 13) states that a number of expectorants are believed to stimulate production of respiratory tract fluid by a reflex action arising from vagal sensory nerve endings of the stomach. Ammonium chloride was one drug studied, but proof of effectiveness is lacking. "AMA Drug Evaluations" (Ref. 5) states that the therapeutic efficacy of ammonium chloride as an expectorant is doubtful. Evidence of effectiveness is sparse and unconvincing.

Cushny (Ref. 12) states that "ammonium chloride can be credited with rendering the mucus secretion of the stomach and bronchi more abundant and less tenacious." No data are offered in support of the contention.

The use of expectorants, including ammonium chloride, appears to be based more on tradition and the widespread clinical impression that they are effective rather than on sound scientific proof (Ref. 5). The Panel believes that ammonium chloride plays an insignificant role in the mouth and throat in the removal of secretions. The effectiveness of ammonium chloride, despite its widespread and long-time use, remains in doubt.

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use up to 150 mg of ammonium chloride in the form of a cough syrup not more than three to four times daily. Use a lozenge containing up to 150 mg of ammonium chloride every 2 hours if necessary. For children under 3 years of age, there is not recommended dosage except under the advice and supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorant active ingredients. (See part IX. paragraph B. 1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. See part IX. paragraph C. below—Data Required for Evaluation.)

References

(1) Swinyard, E. A., and S. C. Harvey, "Diuretic Drugs," *in* "Remington's Pharmaceutical Sciences," 14th Ed., edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 936–937, 1970.

(2) Oppenheimer, D., "Dangers of Acidifying Salt Therapy in Urologic Cases," (abstract), *Journal of the American Medical Association,* 104:864, 1935.

(3) Sievers, M. L., and J. B. Vander, "Toxic Effects of Ammonium Chloride in Cardiac, Renal and Hepatic Disease," *Journal of the American Medical Association,* 161:410–415, 1956.

(4) Sleisenger, M. H., and A. S. Freedberg, "Ammonium Chloride Acidosis: A Report of Six Cases," *Circulation,* 3:837–845, 1951.

(5) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Littleton, MA, pp. 655–658, 1977.

(6) Relman, A. S., P. F. Shelburne, and A. Talman, "Profound Acidosis Resulting From Excessive Ammonium Chloride in Previously Healthy Subjects," *New England Journal of Medicine,* 264:848–852, 1961.

(7) Ticktin, H. E., J. F. Fazekas, and J. M. Evans, "Ammonia Intoxication in a Patient with Congestive Heart Failure Receiving Ammonium Chloride Orally," *The New England Journal of Medicine,* 255:905–907, 1956.

(8) Cass, L. J., and W. S. Frederik, "Comparative Clinical Effectiveness of Cough Medication," *American Practitioner,* 2:844–851, 1951.

(9) Hirsch, S. R., "The Use of Expectorants," *Wisconsin Medical Journal,* 70:153–156, 1971.

(10) Grollman, A., and E. F. Grollman, "Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions," 6th Ed., Lea and Febiger, Philadelphia, p. 995, 1965.

(11) Peach, M. J., "Cations: Calcium, Magnesium, Barium, Lithium, and Ammonium," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 794–795, 1975.

(12) Cushny. A. R., "A Text-Book of Pharmacology and Therapeutics," 9th Ed., Lea and Febiger, Philadelphia, pp. 557–558, 1928.

(13) Goth, A., "Medical Pharmacology: Principles and Concepts," 7th Ed., C. V. Mosby Co., St. Louis, p. 451, 1974.

(14) Krantz, J. C., C. J. Carr, and B. N. La Du, "The Pharmacologic Principles of Medical Practice," 7th Ed., Williams and Wilkins, Baltimore, pp. 824–825, 1969.

(15) Meyer, H. H., and R. Gottlieb, "Pharmacology: Clinical and Experimental," J. B. Lippincott Co., Philadelphia, pp. 342–343, 1914.

b. *Horehound.* The Panel concludes that horehound is safe, but that there are insufficient data to permit final classification of the effectiveness of horehound as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Horehound is an old-time medicine of botanical origin. Horehound (*Marrubium vulgare*) is also known as hoarhound, gypsy wart, harbane, and madwort (Ref. 1). It was official in the "United States Pharmacopeia" from 1820 to 1916 (Ref. 2).

The plant from which horehound is obtained is native to Europe, North Africa, and Western Asia. It has been cultivated in North America. Horehound is a mixture containing a volatile oil, resin, tannin, and a crystalline bitter principle called *Marrubiin.* It has an aromatic odor and a persistent bitter taste (Ref. 1). Hollis, Richards, and Robertson (Ref. 3), concluded that the active ingredient in horehound is a hydroditerpine lactone, whose empirical chemical formula is $C_{21}H_{28}O_4$. The molecular weight of the compound is 344.43. The crystals melt between 150 and 160° F. Horehound is slightly soluble in water, and soluble in alcohol, chloroform, ether, pyridine, phenol, and petrol ether (Ref. 2).

Horehound was once used as a domestic remedy for the treatment of colds and coughs. Earliest documentation of medicinal use cited by Bickerman (Ref. 4) dates back to a 16th century treatise on cough remedies in which horehound was mentioned along with other drugs as a "spurge through the sputa."

Horehound is classed as a stimulant, a diaphoretic, a laxative, and a diuretic (Refs. 2, 5, and 6). Horehound was formerly used as an aromatic,

stomachic, and an expectorant in various forms of bronchitis. Pages and Comte (Ref. 7) reported obtaining beneficial results in the treatment of cardiac extrasystoles using an extract of fresh horehound. The dried plant is of little clinical value.

Horehound was given in the form of a hot infusion, also called a "tea," or as a tincture for its stimulant and diaphoretic effects. The beneficial effects obtained from the use of these old fashioned remedies lie perhaps more in the large draughts of warm water rather than in the traces of volatile oil that they contained. The oil presumably prevents, to some extent, the nausea produced by the warm water alone (Ref. 6). The infusion or tincture can be given cold. It is a bitter tonic once used to treat coughs due to tuberculosis. It was also used as an expectorant in syrups.

Horehound in fusions, or tinctures in hot water sweetened with honey were reported to be beneficial for use in asthma and for treating various inflammations of the lungs and bronchial tubes. A syrup was prepared with honey and kept on hand in many households to loosen phlegm and relieve discomfort caused by coughs and colds (Ref. 5).

When treating deep-seated colds with coughs, horehound was combined with tincture of sculecap (*Scutellaria laterfolia*) and tincture of pleurisy root (*Ascelpias tuberosa*). The combination was administered in warm water.

Horehound in combination with peppermint and spearmint was used for colic and cramps. This combination was also administered in hot water and given as frequently as necessary (Ref. 5).

The above historical account of the use of horehound for treating respiratory infections is of interest, but its widespread use was based upon tradition or clinical impression. No data from controlled studies are mentioned in any of these citations.

(1) *Safety.* The Panel concludes that horehound is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

No data are available on the animal and human toxicity of horehound. Adverse effects or cases of poisoning have not been reported despite the fact that it has been used as a medicinal since the 16th century (Ref. 5).

On the basis of long-term use and experience the Panel concludes horehound is safe for OTC use on the mucous membranes of the mouth and throat.

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of horehound as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

One text states that horehound, given orally, was formerly used as an expectorant in various forms of bronchitis, but its use has since "been abandoned by physicians." Another text states that it was dropped from the "Primary List" of drugs in 1910 (Ref. 8). Verbon, as cited by Clymer (Ref. 5), claims that "horehound is an effective expectorant and stimulant in 'breaking up' recent colds, bronchitis, bronchial catarrh, and certain types of asthma where the mucous expectoration can relieve dyspnea, aphonia, and laryngitis." No data from controlled studies are supplied in support of the contention.

The use of expectorants, including horehound, appears to be based more on tradition and the widespread clinical impression that they are effective, rather than on sound scientific proof. The Panel concludes that horehound plays an insignificant role in the mouth and throat in the removal of secretions. The effectiveness of horehound, despite its widespread and long-time use, remains in doubt.

The Panel feels that the available data on the expectorant effects of horehound are insufficient to make an evaluation and that additional data are necessary before it can be classified as a Category I expectorant active ingredient.

(3) *Proposed dosage.* Adults and children 3 years of age and older: For the herb, mix 1 tablespoonful of the herb into 1 or 2 cupfuls of water. Take this mixture orally every 2 to 3 hours. For the tincture, alone, add 20 to 30 drops to water and take this mixture orally ever 2 to 3 hours.

In using an infusion or "tea," 1 tablespoonful of herb is added to a cup of boiling water. Let this steep for half an hour. One tablespoonful, sweetened with honey, is administered as frequently as necessary.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorants active ingredients. (See part IX. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredient. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. (See part IX. paragraph C. below—Data Required for Evaluation.)

References

(1) Solis-Cohen, S., and T. S. Githens, "Pharmacotherapeutics: Materia Medica and Drug Action," D. Appleton and Co., New York, p. 1115, 1928.

(2) Claus, E. P., "Pharmacognosy," 3d Ed., Lea and Febiger, Philadelphia, pp. 217 and 220, 1956.

(3) Hollis, F., J. H. Richards, and A. Robertson, "Marrubiin, a Diterpenoid Lactone," *Nature,* 143:604, 1939.

(4) Bickerman, H. A., "clinical Pharmacology of Antitussive Agents," *Clinical Pharmacology and Therapeutics,* 3:353–368, 1962.

(5) Clymer, R. S., "Nature's Healing Agents," Dorence and Co., Philadephia, pp. 87–88, 101, 102, 111, and 123, 1963.

(6) Cushny, A. R., "A Text-Book of Pharmacology and Therapeutics," 9th Ed., Lea and Febiger, Philadelphia, p. 63, 1928.

(7) Pages, P., and M. Comte, "Un Nouveau Medicament Cardique: le Marrube Blanc, son Action sur l'arythmie Extrasystolique," *Bulletin de la Societe des sciences medicales et biologiques de Montpellier et du Languedoc mediterraneen,* 8:389–394, 1927.

(8) Lloyd, J. U., "Origin and History of All the Pharmacopeial Vegetable Drugs, Chemicals and Preparation: Volume I, Vegetable Drugs," The Caxton Press, Cincinnati, pp. 338–339, 1921.

c. *Tolu balsam.* The Panel concludes that tolu balsam (balsam of tolu, tolu preparations, tolu balsam tincture) is safe, but that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an effective OTC expectorant active ingredient for use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Tolu balsam is an exudate obtained from *Myroxylon balsamum* (linne), a South American tree. Balsams are naturally occurring mixtures of resins, volatile oils, and organic acids. Tolu balsam contains from 12 to 14 percent free cinnamic and benzoic acids, approximately 40 percent benzyl esters of these acids, and approximately 1.5 to 3 percent volatile oils. It is a yellow-brown, semisolid fluid that has an aromatic odor and taste. Tolu balsam is insoluble in water and soluble in alcohol, benzene, chloroform, ether, and almost insoluble in petroleum ether (Refs. 1 and 2).

(1) *Safety.* The Panel concludes that tolu balsam is safe as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth and throat when used within the proposed dosage limit set forth below.

Balsams have been used since antiquity for medicinal purposes. Tolu balsam is a feeble expectorant and has

been used in cough mixtures for many years. It has been administered in oral doses of 0.6 to 2 g. It is used as a tincture, as well as alone as the balsam. Tolu balsam syrup is employed as a vehicle for expectorant drugs, but it has no specific value for this purpose. Tolu balsam has been used in the treatment of tuberculosis, but it is worthless for this purpose (Ref. 2). Tolu balsam has been used by injection, apparently without any harmful effects. There are no animal and human toxicity data available, but it is not considered to have any degree of toxicity (Ref. 3). The toxicity rating, according to Gosselin (Ref. 4), is 3. Balsam tolu syrup has been included in the "National Formulary." It is no longer mentioned in any of the official compendia, the last being the 14th Edition of the "National Formulary" and the 1975 "U. S. Pharmacopeia."

(2) *Effectiveness.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of tolu balsam as an OTC expectorant active ingredient for topical use on the mucous membranes of the mouth or throat when used within the proposed dosage limit set forth below.

Tolu balsam has been employed occasionally in the treatment of contaminated wounds for its stimulating and mild antiseptic action. It has also been used in the treatment of scabies, as an expectorant in inhalant mixtures for chronic bronchitis, and for the reduction of secretions. The Panel finds no reference to the use of tolu balsam as an expectorant in the teatment of lesions of the mouth or for treating sore throat or other afflictions of the throat (Ref. 2).

(3) *Proposed dosage.* Adults and children 3 years of age and older: Use 0.6 to 2.0 g of tolu balsam per dose in the form of rinses, mouthwashes, sprays, or drops, not more than three to four times daily. Use a lozenge containing 0.6 to 2.0 g of tolu balsam every 2 hours if necessary. For children under 3 years of age there is no recommended dosage except under the supervision of a dentist or physician.

(4) *Labeling.* The Panel recommends the Category I warnings for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.1. above—Category I Labeling.) The Panel proposes the Category III indication for products containing oral health care expectorant active ingredients. (See part IX. paragraph B.3. below—Category III Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC oral health care expectorants. (see part IX. paragraph C. below—Data Required for Evaluation.)

References

(1) Windholz, M., editor, "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 126, 1976.

(2) Osol, A., et al., "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1440, 1955.

(3) Boyd, E. M., "Expectorants and Respiratory Tract Fluids," Pharamacological Reviews, 6:521–542, 1954.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, p. 156, 1976.

Category III Labeling

Proposed indication. "Aids in the removal of secretions and in the temporary relief of discomfort due to occasional sore throat and sore mouth."

C. Data Required for Evaluation

The Panel agrees that the protocols recommended in this document for studies required to bring a Category III drug into Category I are in keeping with the present state of the sciences of pharmacology and therapeutics and the art of medicine and do not preclude the use of any advancements or improvements in methods for obtaining data that might be developed in the future.

1. *General principles in the design of an experimental protocol for testing expectorant drugs.* The effectiveness of a topically applied expectorant is based on its ability to increase the flow of low-viscosity fluid from the salivary and other exocrine glands in the mouth and throat in order to facilitate the removal of inspissated sputum, cellular debris, purulent, and other matter from the mouth and the buccal cavity. Such purulent matter, secretions, and cellular debris often act as foreign bodies on a diseased or otherwise afflicted area and induce stimuli that cause pain and discomfort. Their presence may interfere with the normal spontaneous resolution of a disease process and interfere with healing. By aiding in the removal of such debris and secretions from irritated or ulcerated mucous membranes, expectorants may indirectly ease discomfort due to inflammatory or other pathologic processes. Determination of the increased volume of secretions induced by a topically applied expectorant is not as simple as it would seem. There are no established protocols for testing this category of product. There are no suitable objective methods for making such evaluations. This difficulty stems partly from a lack of basic knowledge concerning the biochemical and physiochemical nature of secretions in pathologic states involving the mouth and throat, as well as changes produced by expectorant drugs. It also stems from lack of knowledge concerning which property of the sputum and other fluids secreted into the mouth and throat correlates best with the ease of expectorant activity.

The volume of fluid secreted in the mouth and throat could be measured using volunteers as subjects. The subject could expectorate the secretions into a receptacle for a selected period of time and the volume, color, viscosity, density, pH, and other chemical and physical characteristics noted to obtain baseline or control data. The drug should be applied as proposed in the labeling and the subject told not to swallow. After the proper time interval necessary for the drug to act has elapsed, the subject could expectorate at selected intervals into a container and the volume, viscosity, and appearance of the fluid observed; the change in volume and other parameters resulting from the drug's action could be compared with those noted in the control. Trotti and Adriani (Ref. 1) measured secretory activity of the buccal glands and the salivary glands by applying strips of pure cotton that had been previously weighed, in the oral cavity between the cheek and the gingiva. The cotton absorbed the secreted fluids. These cotton strips were removed after 15 minutes and the gain in weight was determined to obtain the control value of normally secreted fluid. The process was repeated at 15 minute intervals after administration of the test drug until the secretory activity of the buccal and salivary glands returned to the control level. Subjects participating in a study of topical effect of expectorants must be cautioned not to swallow the drug since it may be absorbed and act systemically as well as topically. Similar techniques can be applied using patients with oral and pharyngeal pathologic states. The patient's subjective evalution of the effects of the drug must also be noted and recorded and relied upon for the assessment of expectorant activity.

2. *Selection of patients.* When patients are used as subjects, two categories of patient types may be selected. One patient type should be chosen for a cross-over study. This patient type should include subjects with a chronic condition, having a tendency to accumulate secretions in the mouth and throat due to chronic stomatitis, pharyngitis, and other conditions. The second patient type should include subjects with an acute inflammatory response, such as

pharyngitis, tonsillitis, stomatitis, or other oral disease, which produces viscous secretions necessitating the use of an expectorant. Because the production of secretions may be influenced by the diseased state of various organ systems, such as the circulatory, nervous system, or gastrointestinal system, patients with heart failure, renal and other diseases, must be excluded. All efforts should be made to maintain the same relative state of hydration throughout the study using intravenous fluids, if necessary. Patients should not be taking drugs that may affect the secretion of sputum or saliva, such as the anticholinergics, cholinergics, or antihistamines. Nonsmokers are preferable as subjects, but if smokers are used they must have abstained from smoking for at least 24 hours. The impact that environmental factors, such as temperature, humidity, and degree of air pollution might have on secretory activity should be recognized and controlled. As many variable factors as possible should be eliminated.

3. *Methods of study.* The double-blind, cross-over design may be used in patients with chronic oral or pharyngeal diseases accompanied by exudates and secretions. Suitable baseline studies must be performed over a selected period of time, prior to the administration of the test drugs. During this period, the following subjective responses should be noted: ease of expectoration, sensation experienced, effect on symptoms; objective responses such as volume, character of the fluid, color, viscosity, pH, and other parameters the investigator deems necessary should also be observed.

Following the baseline studies, similar observations should be made at appropriate time intervals after the administration of the drug and a placebo. The placebo must be indistinguishable from the test drug. Both are to be administered to subjects in a randomized fashion and at a dose and time sequence recommended in the labeling of the product for OTC use.

A randomized double-blind study, consisting of patients with acute pathologic processes with symptoms localized in the mouth and throat, should also be used. Patients with similar lesions should be considered in groups. The drug and the placebo should be applied in a dose and at a time sequence recommended for a minimum of 3 days. Similar observations as discussed above must be made to evaluate effectiveness. The Panel is aware of the fact that controlled observations made during a prior baseline period might not be obtainable with this type model and that most of the data are subjective and that little or none of it is objective. Many more subjects would be needed in such a study. Individual patient diaries should be kept in which are recorded at the time observations are made, the type of symptoms, their duration and severity, time of observation, date, and other pertinent data. Adverse reactions should be noted. The type, symptoms, duration, treatment, and disposition of the subject should be noted.

4. *Interpretation of the data.* Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories. At least one of these three studies must be of the cross-over technique performed in patients with chronic disease of the oral cavity. Approximately 20 to 30 patients will be required for the cross-over study described above. Because of the marked variability in sputum production in acute oral or pharyngeal conditions, compared to that of chronic conditions, day-to-day observations must be made. Since spontaneous improvement of the symptoms is part of the natural history of the disease process, much larger number of patients, possibly 75 or more, must be studied in this group. The subjective indices to be evaluated can be scored and subjected to statistical analysis. A P value of 0.05 or less should be obtained. Ninety-five percent confidence level means acceptable as evidence of a drug effect when compared with a placebo. All data submitted to the FDA must present both favorable and unfavorable results.

5. *Evaluation of study.* Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in humans relevant to various organ systems, that is, cardiovascular, venous, etc., as described elsewhere. (See part II. paragraph C. above—Determination of Safety and Effectiveness.)

Reference

(1) Trotti, W., and J. Adriani, "A Comparison of the Antisecretory and Vagolytic Effects of the Belladonna Alkaloids and Certain Synthetic Parasympatholytic Drugs," *Surgery*, 44:515–519, 1958.

List of Subjects in 21 CFR Part 356

Over-the-counter drugs.

Therefore, under the Federal Food, Drug and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p) 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding new Part 356, to read as follows:

PART 356—ORAL HEALTH CARE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C [Reserved]

Subpart D—Labeling

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321)p), 352, 355, 371); secs.. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§356.1 Scope.

(a) An over-the-counter oral health care drug product in a form suitable for topical administration is generally recognied as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

(b) references in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 356.3 Definitions.

As used in this part:

(a) *Oral health care duug.* A drug product applied topically for the proper care of the mouth, including the temporary relief of symptons of the mouth and throat, for example, occasional minor sore throat or mouth soreness.

(b) *Anesthetic/analgesic.* A substance applied topically to an epithelial surface (e.g., skin or mucous membrane) that relieves pain without necessarily abolishing other sensations (analgesic) or a substance applied topically that completely blocks pain receptors resulting in a sensation of numbness and abolition of response to painful stimuli (anesthetic).

(c) *Antimicrobial agent.* A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction and contributes to claimed effects of the product in which it is included.

(d) *Astringent.* An agent that causes contraction of the tissues or arrest of secretions by coagulation of proteins on a cell surface.

(e) *Debriding agent.* An agent which causes the removal of foreign material or devitalized or contaminated tissue from or adjacent to a traumatic or infected lesion to expose surrounding healthy tissue.

(f) *Decongestant.* An agent that reduces congestion or swelling. In over-the-counter use on mucous membranes the term generally refers to adrenergic drugs that act by vasoconstriction.

(g) *Demulcent.* A bland, inert agent that soothes and relieves irritation of inflamed or abraded surfaces such as mucous membranes.

(h) *Expectorant.* An agent that promotes the expectoration (spitting) of mucus or of respiratory tract secretions by decreasing the viscosity.

(i) *Gargle.* A fluid, usually flavored or medicated or both, but not necessarily so, which is intended to be used to rinse or bathe the posterior part of the oral cavity, with the additional intent to expel mucus from the throat.

(j) *Mouthwash (rinse).* A solution used for rinsing the mouth, not necessarily for medicinal purposes.

(k) *Oral cavity (mouth).* The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands where ducts open into it, the teeth, and the tongue.

Subpart B—Active Ingredients

§ 356.10 Anesthetic/analgesic active ingredients.

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredient:

(a) Aspirin.
(b) Benzocaine.
(c) Benzyl alcohol.
(d) Dyclonine hydrochloride.
(e) Hexylresorcinol.
(f) Menthol.
(g) Phenol.
(h) Phenolate sodium.
(i) Salicyl alcohol.

§ 356.11 Antimicrobial active ingredients. [Reserved]

§ 356.12 Astringent active ingredients.

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredients:

(a) Alum.
(b) Zinc chloride.

§ 356.14 Debriding agent active ingredients.

The active ingredients of the product may consist of any of the following whenused within the dosage limits established for each ingredient:

(a) Carbamide peroxide.
(b) Hydrogen peroxide.
(c) Sodium bicarbonate.

§ 356.15 Decongestant active ingredients. [Reserved]

§ 356.16 Demulcent active ingredients.

The active ingredients of the product may consist of any of the following when used within the dosage limits established for each ingredient:

(a) Elm bark.
(b) Gelatin.
(c) Glycerin.
(d) Pectin.

§ 356.17 Expectorant active ingredients. [Reserved]

§ 356.20 Permitted combinations of active ingredients.

(a) An active ingredient identified in § 356.10, § 356.11, § 356.12, § 356.14, § 356.15, § 356.16, and § 356.17 may be combined with one or more active ingredients from the same section if each active ingredient is present in full therapeutic doses or subtherapeutic doses where a subtherapeutic dose is appropriate, only when there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both.

(b) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11.

(c) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any astringent active ingredient identified in § 356.12.

(d) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any decongestant active ingredient identified in § 356.15.

(e) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any demulcent active ingredient identified in § 356.16.

(f) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any astringent active ingredient identified in § 356.12.

(g) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any decongestant active ingredient identified in §356.15.

(h) Any anesthetic/analgesic active ingredient identified in § 356.10 may be combined with any antimicrobial active ingredient identified in § 356.11 and with any demulcent active ingredient identified in § 356.16.

(i) Any antimicrobial active ingredient identified in § 356.11 may be combined with any astringent active ingredient identified in § 356.12.

(j) Any antimicrobial active ingredient identified in § 356.11 may be combined with any decongestant active ingredient identified in § 356.15.

(k) Any antimicrobial active ingredient identified in § 356.11 may be combined with any demulcent active ingredient identified in § 356.16.

Subpart C [Reserved]

Subpart D—Labeling

§ 356.50 Labeling of anesthetic/analgesic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as follows.

(1) For all products containing aspirin identified in § 356.10(a), the product is identified as an "oral health care analgesic."

(2) For all products containing an ingredient identified in § 356.10(b) through § 356.10(i), the product is identified an an "oral health care anesthetic" or as an "oral health care anesthetic/analgesic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.10.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing aspirin identified in § 356.10(a).* (i) "Do not use if you are sensitive or allergic to aspirin."

(ii) "Do not use if you have a bleeding problem or if you are taking an anticoagulant drug."

(iii) "Do not use without a physician's or dentist's advice if your mouth is highly irritated or ulcerated."

(iv) "Do not use after surgery in the mouth and throat."

(v) "Provide good fluid intake when aspirin or aspirin-containing preparations are used."

(3) *For products containing any ingredient identified in § 356.10 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing aspirin identified in § 356.10(a).* The topical dosage of aspirin is incorporated in a chewing gum base. Adults: chew 420 milligrams of aspirin as needed, not to exceed 3,360 milligrams in 24 hours. Children 6 to under 12 years of age: Chew 210 to 420 milligrams of aspirin as needed, not to exceed 1,680 milligrams in 24 hours. Children 3 to under 6 years of age: Chew 210 milligrams of aspirin as needed, not to exceed 630 milligrams in 24 hours. For children under 3 years of age, there is no recommended dosage except unduer the advice and supervision of a dentist or physician.

(2) *For products containing benzocaine identified in § 356.10(b).* Topical dosage for adults and children 3 years of age and older is a 5- to20-percent solution (spray) or gel used not more than three to four times daily or a lozenge containing 2 to 15 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(3) *For products containing benzyl alcohol identified in § 356.10(c).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 10-percent solution (rinse, mouthwash, spray, or drops) used not more than three to four times daily or a lozenge containing 100 to 500 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For products containing dyclonine hydrochloride identified in § 356.10(d).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 0.10-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 1 to 3 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(5) *For products containing hexylresorcinol identified in § 356.10(e).* Topical dosage for adults and children 3 years of age and older is a 0.05- to 0.1-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 2 to 4 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(6) *For products containing menthol identified in § 356.10(f).* Topical dosage for adults and children 3 years of age and older is a 0.04- to 2.0-percent solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 2 to 20 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(7) *For products containing phenol identified in § 356.10(g).* Topical dosage for adults and children 3 years of age and older is a 0.5- to 1.5-percent aqueous solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 10 to 50 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(8) *For products containing phenolate sodium identified in § 356.10(h).* Topical dosage for adults and children 3 years of age and older is an aqueous solution (rinse, mouthwash, gargle, or spray) containing phenolate sodium equivalent to 0.5 to 1.5 percent phenol used not more than three to four times daily or a lozenge containing phenolate sodium equivalent to 10 to 50 milligrams of phenol taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(9) *For products containing salicyl alcohol identified in § 356.10(i).* Topical dosage for adults and children 3 years of age and older is a 1- to 6-percent aqueous solution (rinse, mouthwash, gargle, or spray) used not more than three to four times daily or a lozenge containing 50 to 100 milligrams taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

§ 356.51 Labeling of antimicrobial drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care antimicrobial."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.11.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.11 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* [Reserved]

§ 356.52 Labeling of astrigent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care astringent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.12.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.12 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing alum identified in § 356.12(a).* Topical dosage for adults and children 3 years of age and older is a 0.2- to 0.5-percent aqueous solution (rinse, gargle, or spray) or swab used not more than three to four time daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing zinc chloride identified in § 356.12(b).* Topical dosage for adults and children 3 years of age and older is a 0.1- to 0.25-percent solution (rinse or mouthwash) or swab used three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

§ 356.54 Labeling of debriding agent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care debriding agent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the removal of phlegm, mucus, or other secretions in the temporary relief of discomfort due to occasional sore throat and sore mouth."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.14.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to childen under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.14 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* The labeling of the products contains the following information under the heading "Directions."

(1) *For products containing carbamide peroxide identified in § 356.14(a).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, gargle, or spray) containing 10 to 15 percent carbamide peroxide in anhydrous glycerin or water used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing hydrogen peroxide identified in § 356.14(b).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, mouthwash, gargle, or spray) containing hydrogen peroxide (3 percent) diluted with an equal part of water or swab used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(3) *For products containing sodium bicarbonate identified in § 356.14(c).* Topical dosage for adults and children 3 years of age and older is a solution (gargle) prepared by combining 5 to 10 percent sodium bicarbonate with one-half teaspoonful of sodium chloride (table salt) in a glass (8 ounces) of warm water used not more than three to four times daily. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

§ 356.55 Labeling of decongestant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care decongestant."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.15.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.15 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(d) *Directions.* [Reserved]

§ 356.56 Labeling of demulcent drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care demulcent."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "Aids in the temporary relief of minor discomfort and protects irritated areas in sore mouth and sore throat."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.16.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.16 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

(3) *For products containing glycerin identified in § 356.16(c).* "Do not use full strength. Dilute with two or three volumes of water."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing elm bark identified in § 356.16(a).* Topical dosage for adults and children 3 years of age and older is a lozenge (agar or water-soluble gum base) containing 10 to 15 percent elm bark taken every 2 hours, if necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(2) *For products containing gelatin identified in § 356.16(b).* Topical dosage for adults and children 3 years of age and older is a 5- to 10-percent aqueous solution (rinse, gargle, or spray), swab, or lozenge or gel containing a sufficient quantity to form a solid or semisolid state used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice of a dentist or physician.

(3) *For products containing glycerin identified in § 356.16(c).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, mouthwash, or spray) or swab containing glycerin diluted with 2 or 3 parts of water used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For products containing pectin identified in § 356.16(d).* Topical dosage for adults and children 3 years of age and older is a solution (rinse, gargle, or spray), swab, or lozenge or gel in quantities sufficient to form a solid or semisolid state, used as often as necessary. For children under 3 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

§ 356.57 Labeling of expectorant drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral health care expectorant."

(b) *Indications.* [Reserved]

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For all products containing any ingredient identified in § 356.17.* (i) "Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by a physician."

(ii) "Discontinue use and consult a physician if irritation persists or increases, or a rash appears on the skin."

(2) *For products containing any ingredient identified in § 356.17 when used in the form of gargles, mouthwashes, or rinses.* "Try to avoid swallowing this product."

Interested persons may, on or before August 23, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before September 22, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: May 13, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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